Intramural Clinical Trial Protocol Template Instructions

Instructions Manual

The goal of this manual is to provide guidance in the creation of a clinical trial protocol utilizing the NIAID intramural protocol template.

The organization of the manual combines the shell of the protocol template (with elements such as the table of contents, section headers, and appendices), with sample language, instructions and hyperlinks to resources.

A number of typographic and layout styles have been utilized in this manual, to assist in distinguishing types of information.

- Regular font Arial: indicates sample language.
- *Italicized Times New Roman:* indicates instructions or guidance.
- *Underlined blue italicized font*: indicates a hyperlink to a resource or a cross-referenced section of the document. To access a link, place the mouse on the underlined text and hit Ctrl + Click.
- Each section will start with sample language (if applicable), followed by instructions or guidance.

Template Documents

There are two templates:

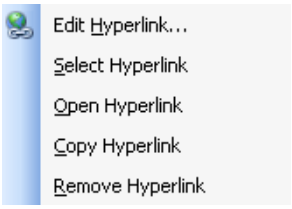
The “CT Template - Blank” template contains only required ethics and safety language and may be preferred by more experienced investigators.

The “CT Template - Sample Language” template contains sample language presented here, in addition to the required safety and ethics language. Note that sample language *is suggested language only, and should be removed or modified by the investigator as applicable to the protocol*.

The templates provide a general format applicable to natural history research protocols. The templates are located on the DCR website under Clinical Research toolkit. The templates are composed table of contents, section headers, appendices. Where applicable, section headings should be preserved in the protocol document in the same order as provided in the template. If a particular section header is not applicable to the protocol, please delete it. However, please do not change the order of the sections, even if the section numbering changes. Please *do* change the Version date and number as applicable, for the final protocol document. Note that the Protocol Template version is on the title page and that the protocol version placeholder follows in the header area of the remaining pages.

Typographic and layout styles have also been employed in the template documents:

- Regular font Arial: indicates core document and sample language.
- *Italicized Times New Roman:* indicates instructions or placeholders and should be deleted from the final protocol.
- [Bracketed items] or XX: indicate placeholders and should be replaced or deleted as appropriate.
- *Underlined blue italicized font*: indicates a hyperlink to a resource or a cross-referenced section of the document. To access a link, place the mouse on the underlined text and hit Ctrl + Click. To change or remove a link, highlight the underlined text + Right Click and select the desired action:



How to save the template as a Word Document:

- Double click the template on the website
- Click **File/Save As.**
- When the **Save As** dialog box opens, rename the protocol document and change **Files of type…** to **Word Document (*.doc),** click **Save.**

How to save the template to your local computer (if you are using a PC):

- Double click the template on the website
- Click **File/New** (*do not* click the  icon). A **New Document** dialog box will open on the right-hand side of the screen.
- Under **Templates**, click 

, a **Template** dialog box will open. Rename the template something that is easy to remember.
- The next time you wish to open a template rather than a document, click **File/Open**, change **Files of type…** to **Document Templates (*.dot),** click **Open.**
- Modify the protocol template to create a new similar protocol, making sure to rename it following the instructions above.

It is anticipated that the templates will be modified based on changes in regulations and user input, with new versions coming out about once a year. Other protocol templates will also be developed as necessary. Your feed-back is valued; please refer questions or comments regarding use of these protocol templates to Heather Bridge at 301-451-2419.

Title

(FULL PROTOCOL TITLE)

The title should be easy to remember, recognizable by administrative support staff, and sufficiently different from other protocol titles to avoid confusion. Brevity with specificity is the goal, be sure to include identifying key words.

NIAID Protocol Number: ##-I-A/N###

This number is assigned by the Office of Protocol Services (OPS) after approved by the Clinical Center Director. The first two digits represent the fiscal year in which the protocol is approved; the letter(s) represent the Institute abbreviation ("I" for NIAID, or "CC" for Clinical Center) and the last four digits represent the next available sequential number for new protocols in that fiscal year (A/N stands for alphanumeric, protocols conducted intramurally will have four numbers, protocols IDs with an "N" in the first position indicate that the protocol will only be conducted offsite). The first protocol version submitted to the IRB will not have a protocol number. However, a version description is recommended. Examples of version descriptions are "Initial IRB Submission" or "Response to IRB stipulations".

Sponsored by:
National Institute of Allergy and Infectious Diseases (NIAID)

Pharmaceutical Support Provided by: *(if applicable)*

Other Identifying Numbers:

IND Sponsor: *(if applicable)*

If the research protocol involves the use of an investigational drug or an investigational device the Regulatory Compliance and Human Subjects Protection Branch (RCHSPB) can file the appropriate paperwork and hold the IDE or the IND, or they can help with these tasks. RCHSPB can also serve as a liaison between the investigator and the FDA, for more information go to the RCHSPB portal/Investigational New Drug Management.

IND

[INVESTIGATIONAL AGENT] Provided by:

List the name of the pharmaceutical company or device manufacturer providing product.

Principal Investigator:

Draft or Version Number:

All versions should have a version number (v.1.0 beginning with the approved initial review) and a submission date. To see the Memo from the Clinical Director go to the NIAID DCR IRB portal/Clinical Research Guidance/Guidance for Investigators/Protocol Requirements (04-27-01), to see the latest Version Control guidance document go to the RCHSPB portal/Clinical Trials Management (Monitoring)/Protocol Version Control,

Version Date

Use the international date format (day month year) and write out the month, e.g., 23 June 2005.

Medical Monitor: *(if applicable)*

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from NIAID (or others, as applicable), unless it is necessary to obtain informed consent from potential study participants.

This template is adapted from the ICH guidance document E6 (Good Clinical Practices), Section 6.

Statement of Compliance

(*Sample Language*)
The study will be conducted in accordance with the design and specific provisions of this IRB approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirement(s). The Principal Investigator will assure that no deviation from, or changes to; the protocol will take place without prior agreement from the sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the trial participants. The Principal Investigator will promptly report to the IRB and the sponsor any changes in research activity and all unanticipated problems involving risk to human subjects, or others.

Provide a statement that the trial will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and the applicable regulatory requirements. Use the applicable regulations and requirements depending on study location and sponsor requirements. Examples of requirements that are potentially applicable include:

- *U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46 and 21 CFR including parts 50 and 56 concerning informed consent and IRB regulations, if under IND, 21 CFR 312).*
- *Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use as amended by Commission Directive 2005/28/EC .*

TABLE OF CONTENTS

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This list should be modified to include protocol-specific terms. Review the sample list of abbreviations, insert additional abbreviations and remove non-applicable abbreviations. To edit this table:

- *To remove a row from the table: Highlight the desired row and Right Click; Select "Delete cells…" Select "Delete entire row".*
- *To add a row to the table: Highlight the desired row; On the menu bar, select "Table"; Select "Insert"; Select either "Rows Above" or "Rows Below".*

List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendment of 1988
COI	Conflict of Interest
CONSORT	Consolidated Standards of Reporting Trials
CRADA	Cooperative Research and Development Agreement
CRF	Case Report Form
CRO	Contract Research Organization
CRIMSON	Clinical Research Information Management System of the NIAID
DCR	Division of Clinical Research
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MedDRA ©	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures/Manual of Operations
N	Number (typically refers to participants)
NCI	National Cancer Institute, NIH
NDA	New Drug Application
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research

PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
RCHSPB	Regulatory Compliance and Human Subjects Protection Branch
RCHSPP	Regulatory Compliance and Human Subjects Protection Program
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
WHO	World Health Organization

Protocol Summary

Limit Protocol Summary to 2 pages.

Full Title:	*Enter the full title*
Short Title:	*Must be 30 characters or less (count must include spaces). To check count: Select "Tools" from the menu bar; Select "Word Count"; Read "Characters (with spaces)"*
Clinical Phase:	*I, II, III, or IV*
IND Sponsor:	*Name of IND Sponsor (if applicable).*
Conducted by:	*Name of Network or Program*
Principal Investigator:	*Name of Principal Investigator*
Sample Size:	N= If *more than one cohort also indicate sample size per cohort.*
Accrual Ceiling:	*Include sample size plus an estimate for screening failures.*
Study Population:	*Include a brief description such as health status (e.g., healthy volunteers or HIV-positive), gender, age, etc.*
Accrual Period:	*Length of time to completely enroll the study. May include a projected start date.*
Study Design:	*Provide an overview of the study design, including description of study type (e.g., double-masked, placebo-controlled, open label, dose-finding, parallel or crossover design, randomized), study arms, sample size and schedule of interventions (e.g., vaccine administration), if applicable*
Study Duration:	Start Date: End Date: *Provide* the *total length of time participants will be on study (intervention + follow-up,) include a projected end date.*
Study Agent/ Intervention Description:	*Include name, dose, duration frequency, and route of administration, if applicable*
Primary Objective:	*Include primary outcome measures and method by which outcomes will be determined.*
Secondary Objectives:	*Include secondary outcome measures and method by which outcomes will be determined.*
Exploratory Objectives:	*(If applicable) Include exploratory outcome measure(s) that may ask separate research questions from the parent protocol.*
Endpoints:	*Include the primary measurements and endpoints used to determine efficacy.*

Précis

Attach a one paragraph (<400 words) summary of the study objectives, study design, and outcome measures.

Schematic of Study Design

Schematic of study design is a diagram that provides a quick "snapshot" of the study. Below are examples of schematics. Select one of the sample styles below and create a schematic that is appropriate for the protocol.

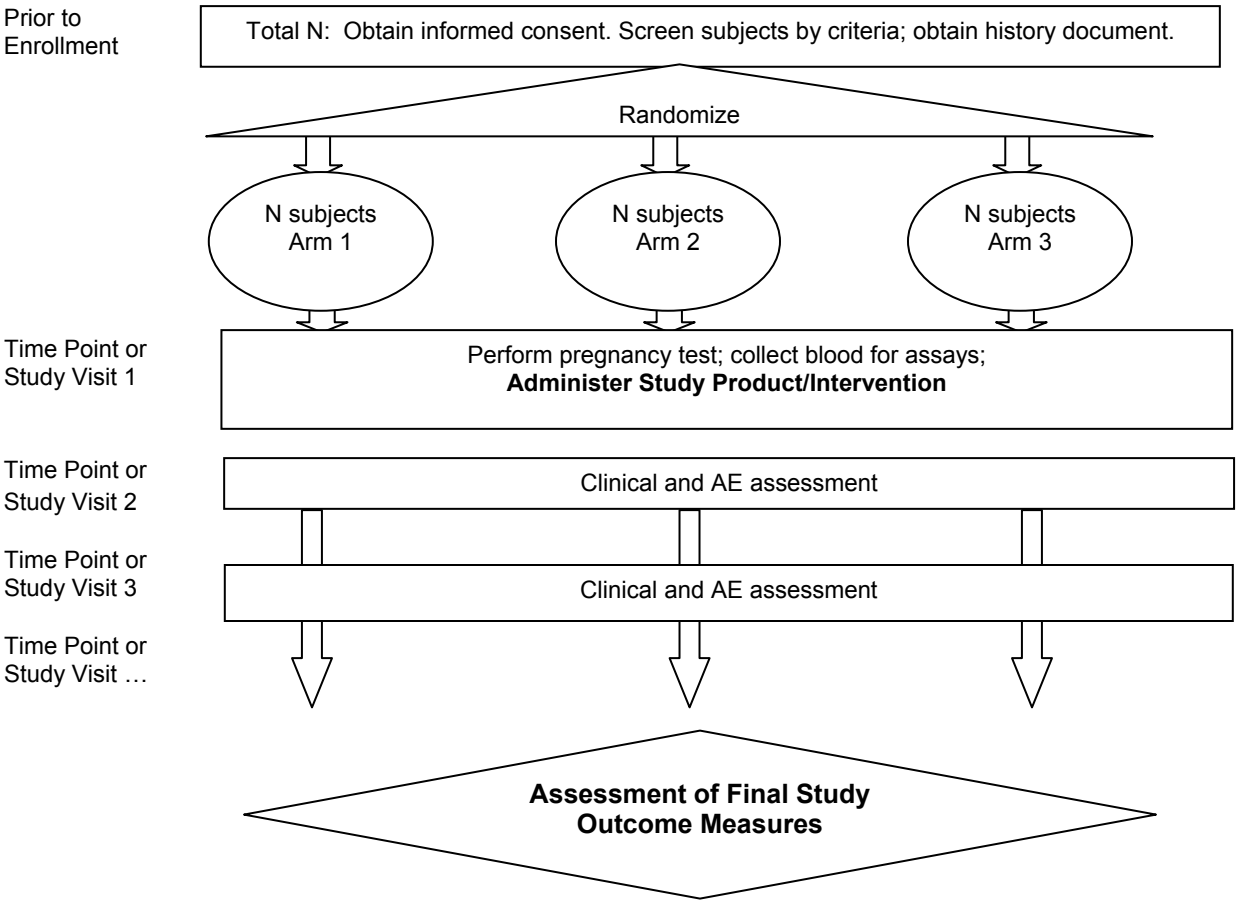
Example #1: Table format: *(e.g., dose escalation)*

Cohort A	ARM 1	Sample Size	Intervention 1
	ARM 2	Sample Size	Intervention 2

Include instructions for progressing to next phase (if applicable): Interim Analysis

Cohort B	ARM 1	Sample Size	Intervention 1
	ARM 2	Sample Size	Intervention 2

Example #2: Flow diagram:



1 Key Roles

(*Sample Language*)
For questions regarding this protocol, contact [name of appropriate NIAID staff] Branch/Division/NIAID [contact information].

***A. Required Elements**:*

Institutions:

Sponsor(s), Medical Monitor (if applicable), Study sites, Clinical laboratory (ies) and other medical or technical departments and/or institutions.

Provide the following information for each organization or institution:

Institution
Address
Contact Person
Phone Number
Fax Number
E-mail address

Investigators:

Principal Investigator (responsible for conducting the trial), Medical Advisory Investigator (qualified physician who is responsible for all trial-site related medical decisions), Lead Associate Investigator, Associate Investigators, Offsite Principal Investigators

Provide the following information for each individual:

Name, degree, title
Institution
Address
Phone Number
Fax Number
E-mail

***B. Optional Elements:** (consider listing, for example):*

Major International Collaborators, (if not included as site principal investigators)
Protocol Statistician(s)

Other study staff should be listed in a separate document (e.g., the Manual of Procedures) as a contact list.

2 Background Information and Scientific Rationale

2.1 Background Information

Write the background in a manner that can be used in the resultant manuscript, include:

- *The name and description of the study agent/intervention(s)*
- *Applicable clinical, epidemiological or public health background or context of the disease under study. Include a brief description of where the research is to be conducted and the relevant demographic and epidemiological information about the country or region concerned, if applicable.*
- *Importance of the study and any relevant treatment issues or controversies*
- *A discussion of important literature and data that are relevant to the trial and that provide background for the trial*
- *A focus on new information to explain the study in the context of a rapidly changing field*
- *An explanation of how this product differs from other available interventions*

2.1.1 Description of the Study Agent/Intervention(s)

This description is in more basic, general terms than Section 6 where the detailed pharmaceutical information is provided. It is intended to provide context for the pre-clinical and clinical studies that follow. This description should be brief and compatible with, but not duplicative of Section 6.

2.1.2 Summary of Previous Pre-clinical Studies

This is a summary of findings from non-clinical studies that have potential clinical significance.

2.1.3 Summary of Relevant Clinical Studies

This is a summary of findings from clinical trials that are relevant to the proposed trial. Provide the scientific and medical data (e.g., results of Phase I and Phase II studies) that justifies the study, its design, and the intervention groups. Be sure to include the references in Appendix A.

2.1.4 Summary of Epidemiological Data

2.2 Rationale

Include a statement of the hypothesis and briefly summarize the natural history of the disorder being studied. Include a description of and justification for the study and its design, including route of administration, dosage, dosage regimen, dosage duration, intervention periods, and selection of study population. Justify any aspects of the study

not approved by regional control authorities (e.g., different dosing schedule, new combination of drugs, new drug formulation, and new population)

2.3 Potential Risks and Benefits

Include a discussion of known and potential risks and benefits, if any, to human subjects.

2.3.1 Potential Risks

Describe in detail any physical, psychological, social, legal, and economic or any other risks to subjects that are immediate risks and long-range risks. For example: long-range risks such as teratogenicity, psychological concerns such as pain or anxiety or practical concerns such as loss of income or mobility.

Discuss rationale for the necessity of such risks, alternative data gathering procedures that have been considered or will be considered, why alternative procedures may not be feasible and why the value of the information to be gained may outweigh the risks involved. For drug studies, refer to the package insert information or the investigator's brochure.

2.3.2 Potential Benefits

For drug studies, refer to the package insert information or the investigator's brochure, but does not need to be included unless there is a new, significant change.

3 Study Objectives

*A detailed description of the **primary, secondary, and exploratory** objectives of the study is included in this section. These typically include:*

- *Statement of purpose: e.g., to assess, to determine, to compare, to evaluate, to define*
- *General purpose, e.g., efficacy, safety, immunogenicity, pharmacokinetics*
- *Specific purpose, e.g., dose-response, superiority to placebo*
- *Method of assessing how the objective is met, i.e., the study outcome measures*

3.1 Primary Objective

The primary objective must match the one used in the Statistical Design section. These objectives determine study design and size and there should be adequate power to achieve an answer.

3.2 Secondary Objectives

May or may not be hypothesis-driven and may include more general, non-experimental objectives (e.g.: To develop a registry or to collect natural history data.) Secondary objectives require an analysis plan, but the size of the trial is not based on a predicted statistical power to achieve the objectives. Secondary objectives should not overshadow

or impede the primary objective and impact on implementation should be taken into consideration.

3.3 Exploratory Objectives

These objectives represent questions of interest, but it is not known a priori whether the study will be designed or sized in a way to achieve an answer

4 Study Design

4.1 Description of the Study Design

A description of the trial design should be consistent with the Protocol Summary and include:

- *A description of the type/design of trial to be conducted (e.g., placebo-controlled, double-mask, parallel design, open-label, dose escalation, dose-ranging)*
- *Phase of the trial*
- *The number of study groups/arms*
- *Single or multi-center*
- *Healthy or sick population*
- *In-patient or out-patient*
- *Description of study groups/arms including sample size (include a table, if appropriate)*
- *Approximate time to complete study enrollment*
- *The expected duration of subject participation*
- *A description of the sequence and duration of all trial periods, including follow-up (specify individual participants vs. entire trial)*
- *Name of study agent/intervention(s)*
- *Changes in scheduling, such as dose escalations*
- *Any stratifications*
- *Methods for collecting data for assessment of study objectives*
- *A specific statement of the primary and secondary outcomes to be measured during the trial (must be consistent with Study Objectives, as stated in Section 3)*
- *Other protocol-specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical scans)*

4.2 Study Endpoints

4.2.1 Primary Endpoint

The primary measurement and endpoint used to determine primary efficacy should be clearly specified. Although the critical efficacy measurements may seem obvious, when there are multiple variables or when variables are measured repeatedly, the protocol should be linked to achieving the primary objective in the statistical plan with an explanation of why they were chosen or designate the pattern of significant findings or other method of combining information that would be interpreted as supporting efficacy.

4.2.2 Secondary Endpoints

4.2.3 Exploratory Endpoints

4.2.4 Substudy Endpoints

5 Study Population

The study population and inclusion/exclusion criteria should be clearly defined in this section of the protocol. The inclusion and exclusion criteria should provide a definition of participant characteristics required for study entry. Careful consideration should be given to the need to achieve that delicate balance of the specificity of criteria, while allowing room for investigator judgment with the overall goal of not inadvertently excluding someone who is a good candidate or allowing enrollment of someone who is not a good candidate for the study.

Include a discussion of recruitment and retention strategies as related to achieving NIH gender/minority guidelines.

- *Retention Procedures: Identify strategies for subject retention.*
- *If women, minorities and children will not be recruited, explain why not. Refer to: http://ohsr.od.nih.gov/info/sheet11.html*
- *If the study intends to enroll children, pregnant women, or other vulnerable populations, please see applicable sections of 45 CFR 46:*
    - *Subpart B: Additional DHHS Protections Pertaining to Research, Development and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization,*
    - *Subpart C : Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects*
    - *Subpart D: Additional DHHS Protections in Children Involved as Subjects in Research.*

- *For research involving children, go to the NIAID DCR IRB portal/Clinical Research Guidance/Guidance for Investigators/Inclusion of Children in Research.*

- *Indicate from where the study population will be drawn (e.g., in-patient hospital setting, out-patient clinics, student health service). Where appropriate (single center studies), include names of hospitals, clinics, etc.*
- *Provide the target/proposed sample size; include estimates for dropouts.*
- *Projected Enrollment and Rationale: Indicate the maximum number of subjects to be enrolled in the protocol. The number should be as precise as possible and supported by appropriate statistics. This number should include participants screened and enrolled (accrued) in the protocol. Investigators should take into account subjects who may sign the consent, but not participate in the investigational portion of the protocol (i.e. screening failures). Any adjustments to the accrual ceiling after initial approval by the IRB must be reviewed and approved by the IRB. Note that a participant is considered "enrolled" if s/he signs a consent document.*
- *Projected Enrollment per Site, (if applicable): Use "approximately" to avoid any possibility of a protocol deviation. Must be based on actual potential enrollment from information gathered from the site.*
- *Projected Drop-out Rate: Use a projection based on previous trial data in same or similar population under same/similar conditions and/or treatment. This will also help with the rationale for the anticipated needed enrollment numbers to achieve the number of evaluable subjects.*

5.1 Participant Inclusion Criteria

Provide a statement that participants must meet all of the inclusion criteria to participate in this study and then list each criterion. The same criterion should not be listed as both an inclusion and exclusion criterion.

- *Clinical indicators of current status (obtained within a set pre-determined number of days prior to randomization)*
- *Prior therapy if any. Consider listing specific prior treatments. Consider listing the allowable duration of prior therapy for the specific population to be studied (e.g., treatment-naïve, treatment-experienced or prior-treatment-failed "salvage" subjects).*
- *Demographic characteristics (e.g., gender, minimum and maximum age) as applicable*
- *Requirements (if any) for birth control*

Examples include the following: informed consent obtained and signed, age, presence or absence of a medical condition/disease, required laboratory result, understanding of study procedures, ability to comply with study procedures for the entire length of the

study, requirements for agreement to avoid conception, etc… If men and women of reproductive capability will be enrolled, include details of allowable contraception methods for trial (e.g., licensed hormonal methods).

5.2 Participant Exclusion Criteria

Provide a statement that all participants meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion.

Examples include the following: medical condition or laboratory finding that precludes participation, recent (with time frame) febrile illness that precludes or delays participation, pregnancy or breastfeeding, characteristics of household or close contacts (e.g., household contacts who are immunocompromised), known allergic reactions to components of the study agent(s), treatment with another investigational drug (with time frame), history of drug/alcohol abuse, receipt of prohibited concomitant medications, etc.

- *List specific clinical contraindications. Specify grades of signs/symptoms. Clinical laboratory indicators of current status, obtained within a set pre-determined days prior to randomization. List the specific tests to be performed and the narrowest acceptable range of laboratory values for exclusion, consistent with safety.*
- *For drug studies: Allergy/sensitivity to study drugs or their formulations.*
- *Specify active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.*
- *Specify inability or unwillingness of subject or legal guardian/representative to give written informed consent.*
- *Specify any clinical (e.g., life expectancy, co-existing disease), demographic (e.g., age) or other characteristic that precludes appropriate diagnosis, treatment or follow-up in the trial. State reason for age restriction.*

Participation of Women:

- **Contraception:** *(if applicable)*

(*Sample Language*)

The effects of [Study Agent/Intervention] on the developing human fetus are unknown. For this reason, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Females of childbearing-age will have a pregnancy test prior to receiving [Study Agent/Intervention]. Should a woman become pregnant or suspects she is pregnant while participating in this study, she should inform study staff and her primary care physician immediately.

(Sample Language for Category C Drugs - when drug specifies the use of two contraceptive methods, Category D Drugs – Possible Fetal Risk or Category X Drugs – Known Teratogens)

The fetal risks associated with [Study Agent/Intervention] are not known, but pre-clinical animal data demonstrate some risk. Subjects must agree not to become pregnant or impregnate a female. Females of childbearing potential must have a

pregnancy test before each dose of study agent. Because of the risk involved, subjects and their partners must use two methods of birth control. They must continue to use both methods until [XX] months after stopping study drug. Two of the birth control methods listed below may be chosen:

- Hormonal contraception
- Male or female condoms with or without a spermicidal
- Diaphragm or cervical cap with a spermicidal
- Intrauterine device (IUD)

- **Pregnancy:** *(if applicable)*

(Sample Language)
Pregnant women are excluded from this study because the effects of [Study Agent/Intervention] on the developing human fetus are unknown with the potential for teratogenic or abortifacient effects.

State the study's pregnancy-related policy and rationale. Specify any exclusion related to pregnancy or plans to become pregnant. Specify methods for assessing current status and willingness to use contraception, if applicable. Provide justification for exclusion in Ethics/Protection of Human Subjects section. To learn more about special protections for pregnant women and fetuses refer to 45 CFR 46, Subpart B.

- **Breast-feeding:** *(if applicable)*

(Sample Language)
Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with [Study Agent/Intervention], breastfeeding should be discontinued if the mother will be treated with [Study Agent/Intervention].

State the study's breast-feeding related policy and rationale. Provide justification for Exclusion in Ethics/Protection of Human Subjects section.
If women will not be recruited, explain why not. Provide justification for Exclusion in Ethics/Protection of Human Subjects section.

Participation of Minorities: *(if applicable) List any special exclusions/guidelines for this special population if different from other populations. Provide justification for Exclusion in Ethics/Protection of Human Subjects section. If minorities will not be recruited, explain why not or refer to Section 14.*

Participation of Children: *(if applicable)*
(Sample Language)
Subjects younger than 18 years of age will be excluded from the study. Because there are insufficient data regarding dosing or adverse events available in adults to judge the potential risk in children, the study is of "greater than minimal risk"

and does not meet the criterion of 45 CFR 46, Subpart D, governing the participation of children in research.

List any special exclusions/guidelines for this special population if different from adults. Provide justification for exclusion in Ethics/Protection of Human Subjects section. If children will not be recruited, explain why not or refer to Section 14.

Co-enrollment Guidelines: *(if applicable)*
(Sample Language)
Co-enrollment in other trials is restricted, other than for observational studies, or those evaluating the use of a licensed medication. Study staff should be notified of co-enrollment as it may require the approval of the [investigator or medical monitor].

Specify guidelines for co-enrollment. Describe any restrictions or opportunities concerning other studies in which the patient may enroll, while participating in this study.

6 Study Agent/Interventions

Note: *If multiple study agents are to be evaluated in the study, they should be listed in the following subsections for each product and the sections should be renumbered accordingly. Describe placebo or control product within the following subsections, if required.*

Describe the type of control with rationale for choice of control (e.g. placebo, no treatment, active drug, dose-response, historical). Discuss known or potential problems associated with the control group chosen in light of the specific disease and therapies being studied.

6.1 Study Agent Acquisition

6.1.1 Formulation, Packaging, and Labeling

(*Sample Language*)
Each bottle will be individually labeled with the NIAID protocol number, dosing instructions, recommended storage conditions, the name and address of the manufacturer, randomization number, Investigational Use Statement (“Caution: New Drug – Limited by Federal [USA] Law to Investigational Use”) and that the agent should be kept out of reach of children.

Information in this section can usually be obtained from the Investigator’s Brochure (IB) or the package insert. Make the IB or package insert available to all investigators as part of the study’s Manual of Procedures (MOP) or distributed separately, as appropriate. The package insert may be attached as an appendix to the protocol. This section should include the name of the manufacturer of study agent(s) and/or placebo.

6.2 Study Agent Storage and Stability

Describe product's storage needs. Include storage requirements and stability (temperature, humidity, security, and container). Provide additional information regarding stability and expiration time for studies in which multi-dose vials are entered (i.e., the seal is broken).

6.3 Preparation, Administration, and Dosage of Study Agent/Intervention(s)

Include thawing, diluting, mixing, reconstitution/preparation instructions, as appropriate. List study agents, route, doses, duration, and frequency of administration in this section. Include any specific instructions or safety precautions for administration of study products or masking (blinding) of the product for the administrator. Include maximum hold time and conditions of product once thawed, mixed, diluted, reconstituted, etc…

Study Agent

Description

- Dosing and Administration: *Procedures for selecting each patient's dose of test drug/ investigational product and active control/comparator should be described. The timing (time of day, interval) of dosing and the relation of dosing to meals should be described. Any specific instructions to patients about when or how to take the dose(s) should be described. Discuss the maximum hold time once thawed/mixed, if appropriate, before administration.*
- Route of Administration: *Oral, nasal, intramuscular, etc.*
- Starting Dose: *State the starting level of the treatment (or starting dose of the study agent.)*
- Dose Escalation Schedule *(if applicable): Describe the dose escalation scheme and treatment regimen (using exact dose, rather than percentages). State any minimum period required before a subject's dose might be raised to the next higher dose or dose range.*
- Dose Adjustments/Modifications/Delays: *The protocol should state the conditions under which a dose change will be made, particularly in regard to failure to respond, or to toxic or untoward changes in stipulated indicators (e.g., white blood cell count in cancer chemotherapy). The protocol must state explicitly the dose-limiting effects that are anticipated. Provide definitions of endpoints that will be used to determine dose escalations.*
    - *If a subject is responding positively to treatment, the protocol should specify whether treatment would progress to still higher doses. If appropriate, provide a dose de-escalation schema with treatment modifications.*
- Duration of Therapy: *Discuss what will be required for each active phase and what duration is the minimum necessary for an "evaluable" subject.*
- Tracking of Dose: *Discuss what procedures will be in place to monitor dosing for each subject.*

- Limitations on Prior Therapy: *State allowable type and amount of prior therapy. Define as appropriate any limitations on prior therapy and the time from last prior regimen.*
- Use of Ancillary Medications/OTC Products/Foods: *State guidelines for use of appropriate supportive care medications or treatments.*
- Participant Access to Study Agent At Study Closure: *If applicable, describe obligations to continue beneficial interventions after subjects are no longer enrolled in the study.*

Control product *(if applicable)*

Description: *If a placebo is being used in a drug trial, note whether it has similar color, taste, etc..., as the active drug. The source of placebos and active control/comparator product(s) should be provided. Any modification of comparator product(s) from their usual commercial state should be noted, and the steps to be taken to assure that their bioavailability will be unaltered.*

Address the following topics, (if applicable):

- Dosing and Administration
- Route of Administration
- Starting Dose
- Dose Escalation Schedule, if applicable
- Dose Adjustments/Modifications/Delays
- Duration of Therapy
- Tracking of Dose

Include thawing, diluting, mixing, reconstitution/preparation instructions, as appropriate. List study agents, route, doses, duration, and frequency of administration in this section. Include any specific instructions or safety precautions for administration of study products or masking (blinding) of the product for the administrator. Include maximum hold time and conditions of product once thawed, mixed, diluted, reconstituted, etc…

6.4 Study Product Accountability Procedures

Provide plans for how the Study Agent/Intervention(s) will be distributed including participation of a drug repository or pharmacy, frequency of product distribution, amount of product shipped, documentation of adequate and safe handling, and plans for return of unused product.

The investigator must retain all unused or expired product and accounts of any product accidentally or deliberately destroyed until the study monitor has confirmed accountability data. At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6.5 Assessment of Participant Compliance with Study Agent/Intervention(s)

Include plans for compliance assessment in this section. Describe measures to be taken to ensure adherence to treatment/regimens and the documentation necessary, (e.g., questionnaires, direct observation, pill counts, diary cards, etc…). If no such assessment is planned, state why it is not needed or will not be incorporated into the protocol (will be included in the Manual of Operations, for example).

6.6 Concomitant Medications and Procedures

(Sample Language)

All concomitant prescription medications taken during study participation will be recorded [in CRIMSON or] on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications taken at the time of adverse events (all grades).

Permitted medications or drugs/interventions.

Describe any drug interactions and toxicities for standard agents that are likely to be given in conjunction with this protocol. List any storage guidelines, reconstitution guidelines or other special information for non-investigational medications. For injectable medications, describe if topical numbing medications such as Emla cream may be used. Describe any special precautions or warnings that are relevant for agent/device administration (e.g., necessity of administering agent with food, premedications, etc.). Refer to the most recent study medication's package insert or investigator's brochure to access additional current information on prohibited and precautionary medications. Include drugs from the exclusion criteria if they are also prohibited while the subject is on study. Include instructions for dose modification of certain medications, if appropriate. Discuss concomitant medications documentation (e.g., recorded at screening and every study visit). How allowed concomitant therapy might affect the outcome due either to drug-drug interaction or to direct effects on the study endpoints should be discussed, and how the independent effects of concomitant and study therapies could be ascertained should be explained.

6.7 Precautionary and Prohibited Medications and Procedures

Refer to the most recent package insert or investigator's brochure to access additional current information on prohibited and precautionary medications. If applicable, consider attaching the package insert as an appendix to the protocol.

6.7.1 Prohibited Medications and Procedures

(*Sample Language*)
Treatment with [list specific drugs] will not be permitted unless discussed with and approved by the [study medical monitor/sponsor/investigator].

If applicable, list all medications/procedures that are NOT permitted on study. Include drugs from the exclusion criteria if they are also prohibited while the participant is on study.

6.7.2 Precautionary Medications and Procedures

If applicable, list all medications/procedures for which there are precautions for concomitant use with the study products/interventions. Include instructions for dose modification, if appropriate.

6.8 Prophylactic Medications and Procedures

List all medications and/or treatment that will be provided as prophylaxis on study.

6.9 Rescue Medications

List all drugs and/or treatments that may be provided on study for "rescue therapy".
Note: *This section should be consistent with the medications restrictions in the inclusion/exclusion criteria.*

7 Study Procedures/Evaluations

Information outlined in the Procedures/Evaluations section should refer to and be consistent with the information in the Schedule of Procedures/Evaluations in Appendix C.

Study Procedures:

- *Recruitment Procedures: Identify strategies for subject recruitment. Describe the method for identifying and recruiting candidates for the trial. Data should be presented supporting recruitment estimates. Specific goals for women and minority recruitment and plans for achieving those goals must be explicitly stated.*
- *Screening Eligibility/Procedures: Discuss the sequence of events that should occur during screening and decision points regarding eligibility. Mention that procedures will take place only after the informed consent is signed. Describe procedures for documentation of reasons for ineligibility and for nonparticipation of eligible subjects. List the timeframe prior to enrollment within which screening tests and evaluations must be done (e.g., within 28 days prior to enrollment).*
    - *Re-Screening….Describe the conditions and procedures for re-screening.*
- *Run-in Procedures: If a Run-in period is required, describe procedures for Run-in, safety methods and evaluation and if Run-in may be repeated. Mention that procedures will take place only after the informed consent is signed*
- *Enrollment Procedures: Discuss the sequence of events that should occur during enrollment including any baseline procedures. Mention that procedures will take place only after the informed consent is signed If a participant comprehension tool is*

to be used, describe the tool and method of application; for example, a Volunteer Understanding Quiz (VUQ) and method of grading.

- *Study Procedures: Describe in detail study interventions and procedures.*
- *Testing Performed: Clinical (including behavioral), laboratory, and physiological tests and protocols should be described briefly here. More detail can be placed in an appendix.*

7.1 Clinical Evaluations

List all clinical evaluations to be done during the protocol, and provide details/timelines at each visit of what are included and special instructions, if any. Distinguish between standard of care and research procedures and tests.

Examples:

- *Medical History (describe what is included for history, e.g., timeframe considerations, whether history will be obtained by interview or from medical records).*
- *Medications History (e.g., describe if a complete medications history is needed, or if only currently taken medications should be included; prescription medications only or also over-the-counter). Assessment of eligibility should include a review of permitted and prohibited medications.*
- *Physical Exam (list the vital signs and organ systems to be assessed); if appropriate, discuss what constitutes a targeted physical exam and at what visits it may occur. If an Adverse Event occurs, describe if a full physical exam should be done.*
- *Reactogenicity assessments (e.g., pain, tenderness; describe rating scale).*
- *Review of diary cards.*
- *Counseling procedures.*
- *Radiologic procedures (e.g., chest x-rays, DEXA scans, CT scans).*

7.2 Laboratory Evaluations

7.2.1 Clinical and Research Laboratory Evaluations and Specimen Collection

Laboratory Evaluations

List all protocol laboratory evaluations. Include specific test components and type of specimens needed for each test (e.g., plasma or serum). In order to comply with the NIH Clinical Center policy M95-9 on the amount of blood drawn, list the total amount needed for each test. The amount of blood that may be drawn from those persons 18 years of age or older for research purposes shall not exceed 450 ml over any six week period. The

amount of blood to be drawn from volunteers and the frequency of collection shall be specified in the clinical research protocol. For pediatric patients, no more than 3 ml/kg may be drawn for research purposes in a single blood withdrawal, and no more than 7 ml/kg may be drawn over any six-week period.

Examples:

- *Hematology: hemoglobin, hematocrit, WBC with differential, platelet count*
- *Biochemistry: creatinine, total bilirubin, ALT, AST, glucose (fasting/non-fasting)*
- *Urinalysis: dipstick urinalysis, including protein, hemoglobin and glucose; if dipstick is abnormal, complete urinalysis with microscopic is required.*
- *Pregnancy test usually to be done within 24 hours prior to study intervention and results must be available prior to administration of study product.*
- *Biopsy specimens: tissue*

Special Assays or Procedures

List special assays or procedures required to assess the study product (e.g., immunology assays, PK studies, photographs). For laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. For procedures, provide special instructions or precautions. If more than one laboratory will be used, specify which assays or evaluations will be done by each laboratory.

7.2.2 Specimen Preparation, Handling and Shipping

(*Sample Language*)

Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products; appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

Specify laboratory methods (e.g., use consistent laboratory methods throughout the study) to provide for appropriate longitudinal and cross-comparison.

7.2.2.1 Instructions for Specimen Storage

Provide details of proper handling of specimens for long-term storage including logging, databases and tracking. If laboratory procedures are described in an appendix or SOP document, provide specific cross-reference to where this information may be found.

7.2.2.2 Specimen Shipment

Transport of Infectious Agents

(*Sample Language*)

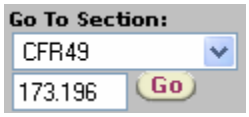
All infectious specimens will be transported using packaging mandated in the Code of Federal Regulations, 42 CFR Part 72 and according to individual carrier guidelines, as applicable.

Refer to Appendix D for full schedule details of specimens and for specimen shipment details including labeling requirements.

Transport of Infectious Agents
All infectious specimens will be transported using packaging mandated in the Code of Federal Regulations, 42 CFR Part 72. If the protocol involves any transport of materials that include infectious substances, diagnostic specimens, toxic chemicals, or hazardous materials then prepare a plan for handling these shipments according to current regulations. Principal Investigators are responsible for knowing about and observing (and ensuring protocol collaborators also comply with) all the regulations for classification, packaging and labeling, permits or authorizations, and personnel training for shipment of biological and hazardous materials required for the conduct of the protocol. Failure to comply with federal and international regulations on shipment of biological or hazardous materials can result in refusal of the carrier to complete the shipment, fines, and/or jail.

The following websites should be consulted for shipping regulations that may apply to the protocol:

- *Department of Transportation, Guide to Changes (Effective October 1, 2006), "Transporting Infectious Substances Safely".*
- *Department of Transportation. 49CFR171-180. Hazardous Materials Definitions: http://www.myregs.com/dotRSPA/ . On the USDOT page, click on DOT Interpretations.* 

- *Hazardous Materials Regulations: http://www.myregs.com/dotRSPA/ . On the USDOT page, enter the section of the regulations you would like to see for example "Infectious Agents" so you would enter, "173.196".*


- *Public Health Service 42CFR72. Interstate Shipment of Etiologic Agents. 42CFR Part 72. Federal Register, Vol. 45, No. 141-Monday, July 21, 1980. http://wonder.cdc.gov/wonder/prevguid/p0000087/p0000087.asp*
- *Dangerous Goods Regulations. International Air Transport Association (IATA). http://www.iata.org and http://www.iata.org/NR/rdonlyres/88834D9F-8EA2-42A0-8DA6-2BED8CD2E744/0/SAMPLEISSG7THED.pdf*

- *Guidelines for the Safe Transport of Infectious Substances and Diagnostic Specimens. World Health Organization, 1997.* *http://www.who.int/csr/emc97_3.pdf*
- *United States Postal Service. DMM 300.601Mailability, Section 10.17* *http://pe.usps.gov/text/dmm300/601.htm#wp1064962*
- Occupational Health and Safety Administration (OSHA). 29CFR1910.1030. Occupational Exposure to Blood borne Pathogens. *http://www.osha.gov/SLTC/bloodbornepathogens/*

7.3 Substudies

Definition: A substudy asks a separate research question from the parent protocol and does not overlap with the parent protocol's objectives, but uses all or a subset of study participants or specimens.

A concept sheet for a proposed substudy should be approved prior to development of a full protocol for the substudy. Once the concept for a substudy is approved, a decision will be made as to whether the concept is appropriate as a substudy or should be a stand-alone study. If a substudy is added to an ongoing parent study at a later time, a protocol amendment is required.

List with brief description:

- *Description of the substudy and its objectives*
- *Impact on the main study*
- *Behavioral issues*

8 Research Use of Stored Human Samples, Specimens or Data

(*If applicable*)

Research often involves the use of stored human specimens or data. Such use obliges research investigators and Institutional Review Boards to consider the rights and welfare of the individuals who provide them, especially when samples retain identifiers or codes. The research use of existing specimens without the ability or intent to identify the source may pose little risk to the donors. However, when these sources can be identified, conflicts may arise between their rights and the scientific benefit that can be obtained from studying their stored samples. For more guidance on Stored Samples refer to OHSR Information Sheets/Forms - Sheet 14 PROCUREMENT AND USE OF HUMAN BIOLOGICAL MATERIALS FOR RESEARCH .

NIH IRB-approved research protocols in which IRP researchers intend to collect and store human specimens or data: New protocols should include this information at the time of initial review. All such protocols must include:

- *Nature of the proposed research*
- *Intended use of the samples;*

- *How they will be stored;*
    - *If coded or unlinked*
        - *If coded a justification for maintaining the code*
        - *Who can link the code to the source*
        - *How confidentiality will be maintained*
- *How they will be tracked;*
- *What circumstances would prompt the PI to report to the IRB loss or destruction of samples;*
- *What will happen to the samples/specimens/data at the completion of the protocol.*

8.1 Use of Stored Samples

(*Sample Language*)
Samples and data collected under this protocol may be used to study [XX]. [No] genetic testing will be performed. *(If applicable:)* Any other research or experimental treatments will be done under this or other protocols for which separate signed informed consent documents will be obtained.

Provide a description of the intended use of the samples, include details such as:

- *Whether they are intended only for study-related usage or if they will be made available for future research.*
- *If intended for future research, specify whether the usage is related to the disease of interest or for any research purpose.*
- *If applicable specify whether and how samples will be provided to a collaborator. If collaboration will take place specify that the appropriate waiver will be obtained for anonymized samples or that the appropriate agreement will be reached through the Office of Technology Development for identified or linked samples.*

8.2 Disposition of Stored Specimens and Data

(*Sample Language*)

Access to stored samples will be limited using [either a locked room or a locked freezer]. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

How they will be stored, if mentioned, refer to Section 7.2.2.1.

- *Whether the samples will be identified or de-identified and coded.*
- *If coded, a justification for retention of the identities or codes of the sources of sample data.*
    - *When codes will be utilized, a description of the ease or difficulty with which linkage can be made between the code and the source.*
- *A description of the extent to which confidentiality will be maintained.*

(*Sample Language*)

Samples and data acquired after [date] will be tracked *[describe method of tracking, such as the name of the software tracking program or other logging/tracking method*].

How they will be tracked, if mentioned, refer to Section 7.2.2.1.

- *Provide a description of who can make the linkage between the code and the source.*

(*Sample Language*)

In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. In that case, IRB approval must be sought prior to any sharing of samples. Any clinical information shared about the sample would similarly require prior IRB approval.

In addition to obtaining IRB approval, prior to collaborating with non-study investigators/collaborators, the investigator should check with the NIAID Office of Technology Development to ensure that all proper agreements are in place.

(*Sample Language*)

At the completion of the protocol (termination), samples and data will either be destroyed, or after IRB approval, transferred to another existing protocol.

D*escribe the disposition of the specimens/samples/data at the completion of the protocol, e.g. it will remain open, they will be sent to a repository, etc… as applicable.*

(*Sample Language*)

Any loss or unanticipated destruction of samples or data that meets the NIH Intramural Protocol Violation definition or results in a violation that compromises the scientific integrity of the data collected for the study; will be reported to the NIAID IRB.

(If applicable)

Additionally, subjects may decide at any point not to have their samples stored. In this case, the principal investigator will destroy all known remaining samples and report what was done to both the subject and to the IRB. This decision will not affect the subject's participation in this protocol or any other protocols at NIH.

What circumstances would prompt the PI to report to the IRB loss or destruction of samples. For example what is the percentage of specimens lost that could threaten the integrity of the study outcome. What is the impact if a freezer should go down and samples are lost; or if samples are unusable due to a misunderstanding of procedures are samples lost or is it safe to redraw and how does that impact the burden on the affected participants? To learn more about what constitutes a protocol violation go to the NIAID DCR IRB portal/IRB Submission Forms/Violations, additional guidance may be found about protocol deviations the NIAID DCR IRB portal/Clinical Research Guidance/Advisories/Reporting of Protocol Deviations.

9 Study Schedule

Information outlined in the Study Schedule section should refer to and be consistent with the information in the Schedule of Procedures/Evaluations in Appendix C.

Allowable windows should be stated for all visits. *To determine the appropriate windows, consider feasibility and relevance of the time point to study outcome measures (e.g., PK studies may allow little or no variation, with required time points measured in minutes or hours, whereas a 6-month follow-up visit might have a window of several weeks).*

The schedule must include not only clinic visits but all other types of contacts, e.g., telephone contacts, scheduled notification letters.

9.1 Screening

(*Sample Language*)
The purpose of the screening visit is to determine volunteer eligibility for study participation. Subjects who are diagnosed with a medical condition during the screening process, (e.g., test positive for hepatitis B, hepatitis C, HIV) will be notified and referred for medical care. The following screening evaluation must be completed in the [XX] days prior to enrollment.

Include only those evaluations necessary to assess whether a participant meets enrollment criteria. Discuss the sequence of events that should occur during screening and the decision points regarding eligibility. List the timeframe prior to enrollment within which screening tests and evaluations must be done (e.g., within 28 days prior to enrollment). Refer to Section 7 Study Procedures/Evaluations for details of clinical evaluations and laboratory evaluations for screening

This section should specify that informed consent must be obtained prior to initiating screening procedures. *Refer to Section 14.3*

9.2 Enrollment/Baseline

(*Sample Language*)
Day 0 is defined as the day of enrollment and first administration of the study agent/intervention. Study participants must sign study participation consent form to be considered enrolled into the trial and must be randomized to a schedule [*if applicable*] and have all study screening complete before the first study agent/intervention is administered. Evaluations prior to the first administration are the baseline for subsequent safety evaluations. Females of reproductive potential must have a negative serum pregnancy test on Day 0 prior to enrollment and on each day of administration of the study agent/intervention.

Discuss evaluations/procedures necessary to assess or confirm whether a participant still meets the eligibility criteria and may be enrolled, and those assessments that are required at baseline for later outcome measure comparison after study intervention (e.g.,

baseline signs and symptoms prior to vaccination). Discuss the sequence of events that should occur during enrollment and/or initial administration of study product. List any special conditions (e.g., results of the pregnancy test must be negative and available prior to administration of study product). List the procedures for administering the study product or intervention, and follow-up procedures after administration (e.g., assessment of vital signs, reactogenicity).

9.3 Active Phase

(Sample Language from Vaccine Trials)

Subjects will receive [study agent] at X, X and X months. The visit and injection schedule is shown in table format in Appendix C. The protocol allows a window of ±X days in scheduling study injection visits as long as there are at least X days between injections. The injection site will alternate either the right or left deltoid muscle as the site for the primary immunization schedule. Following injections, subjects will be observed for a minimum of 60 minutes. Vital signs will be taken at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-injection. If erythema or induration is present, its perpendicular diameters will be measured and recorded at each time point to determine any changes. After an intramuscular injection of [study agent] the subject will be contacted by phone at X days after injection and will have a clinic visit at that time only if indicated by adverse events. Otherwise the subject will have a follow-up visit on the ±X day following injection for clinical laboratory tests (i.e., urinalysis, CBC, differential, platelets, creatinine, ALT, PT/PTT) and photograph of the injection site.

Indicate schedule of evaluations occurring after randomization while the subject is on-study. Include allowable time window in which evaluations may take place; e.g., study visits must be scheduled on the weeks indicated in the Schedule of Evaluations ± 7 days. Discuss the activities immediately before and any follow-up activities that will take place immediately after each study procedure/medication. Discuss how subjects who report a recent or intercurrent illness will be handled (e.g., cold, fever, infection, etc.)

9.4 Follow-up

Include discussion of evaluations/procedures required to assess or confirm study outcome measures and study evaluations. Discuss the sequence of events that should occur during the visit, if applicable. Include, as applicable, counseling, review of reactogenicity, medications, assessment of adverse events, etc.

9.5 Final Study Visit

Define when the final study visit should occur and any special procedures/evaluations or instructions to the participant. Describe provisions for follow-up of ongoing adverse events/serious adverse events.

9.6 Early Termination Visit

Specify which of the evaluations required for the final study visit should be done at a termination visit if early termination occurs and if the participant is willing. Participants may withdraw voluntarily from participation in the study at any time. Participants may also withdraw voluntarily from receiving the study intervention for any reason. Clearly differentiate between what evaluations are to be done in each of these circumstances.

If voluntary withdrawal occurs, the participant should be asked to continue scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the participant's condition becomes stable. Describe efforts to continue follow-up, especially for safety outcome measures.

9.7 Pregnancy Visit

(*If applicable*)
The protocol should address the procedures to be followed if a participant becomes pregnant while on study. Indicate whether the participant will be allowed to continue to receive the study agent/intervention(s).

Provide any other guidance relevant to the study agent and pregnancy and/or breastfeeding.

9.8 Recontact of Subjects After Trial Termination

Discuss whether the protocol requires that subjects be contacted post-study to gather additional information or to possibly re-enroll in another phase of the study. Include the post-study timeframe for recontact (e.g., 5 years following study completion), why the subject would be recontacted, what types of information would be requested and who would be doing the recontacting. Discuss procedures for recontact attempts (e.g., last-known address, phone number, etc.).

10 Assessment of Safety

Reference safety parameters that are outcome measures.

10.1 Specification of Safety Parameters

Include this section if safety is not a primary study outcome measure.

10.2 Definition of an Adverse Event (AE)

(*Sample Language*)
An adverse event (AE) is any unanticipated or unintended medical occurrence or worsening of a sign or symptom (including an abnormal laboratory finding) or disease in a study participant, which does not necessarily have a causal relationship with the study condition, procedures or study agent(s), that occurs after the informed consent is obtained.

Pre-existing conditions or illnesses which are expected to exacerbate or worsen are not considered adverse events and will be accounted for in the subject's medical history

(*Sample Language for Vaccine Studies and Some Therapeutic Trials)*

Reactogenicity: Reactogenicity events are adverse events that are common and known to occur for the Study Agent(s)/Intervention(s) being studied and should be collected in a standard, systematic format using a graded scale based on functional assessment or magnitude of reaction.

Provide a definition, specific to this protocol, of the expected vs. unexpected AEs, based on the risk profile of the Study Agent(s)/Intervention(s)(refer to the IB or package insert) and/or disease process.

Note that adverse events should be tracked starting with the initial consent through the end of study follow-up.

10.3 Definition of a Serious Adverse Event (SAE)

(*Sample Language*)
Serious Adverse Event (SAE): A Serious Adverse Event is defined as an AE meeting one of the following outcomes:

- Death during the period of protocol defined surveillance
- Life Threatening Event (defined as a participant at immediate risk of death at the time of the event)
- Inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity

Any other important medical event that may not result in one of the above outcomes, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

(*Additional sample language, applicable for an IDE protocol*)
An unanticipated adverse device effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

This language is based on FDA regulation (21 CFR 812.3(s)) and is only applicable for those studies involving an investigational device.

Consider the context of the trial and adjust reporting procedures appropriately for the study population and agent/intervention(s) being studied. Define the circumstances (for instance, severity grades >2) in which abnormal laboratory values will be reported as AEs/SAEs. Generally, in healthy people, a grade 3 or above abnormality is an SAE. In sick populations, define in terms of a change from baseline and disease progression.

10.4 Methods and Timing for Assessing, Recording, and Analyzing, Managing Safety Parameters

This section should be based on the risk profile of the Study Agent(s)/Intervention(s). Include a review of relevant literature, which should be referenced. Add relevant websites, etc. from which the information could be drawn.

If a package insert is available, it should be used as the primary source of risk information. If the study agent is investigational, the IB should be the primary source of the risk information. In addition, literature searches can also provide relevant risk information. If the risk profile cannot be described from any of the above sources, the risk information discussion will result from the literature search and review

10.4.1 Methods and Timing for Assessment

Describe the means of obtaining adverse event data. Describe which adverse events will be collected as solicited events and the format used to capture the solicited event (checklist, structured questioning, diary, etc), and any specific rating scale if one is to be used. Describe how unsolicited events will be captured. Describe the time period for adverse event collection.

10.4.1.1 AE/SAE Grading and Relationship Assignment

Intensity (severity) Scale

(*Sample Language*)
Each adverse event will be graded according to the Table for Grading Severity of Adverse Events (see Appendix B). All other laboratory and clinical AEs that occur in a subject, will be assessed for severity and classified into one the categories below.

- **Grade 1 (Mild)**: event requires minimal or no treatment and do not interfere with the patient's daily activities.
- **Grade 2 (Moderate)**: event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3 (Severe)**: event interrupts a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

- **Grade 4 (Life threatening)**: Any adverse drug experience that places the patient or participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.
- **Grade 5 (Death)**

Assessment should include the intensity (severity) of the event whether clinical or laboratory and the relationship to Study Agent(s)/Intervention(s). (Collection of laboratory data should be limited to those laboratory parameters that are relevant to safety, study outcome measures and/or clinical outcome.)

Intensity will be assigned using a protocol defined grading system. The Toxicity Tables (grading system) will define what values or clinical findings are considered abnormal. Reference tables for laboratory/clinical events APPENDIX C & APPENDIX B, (Selection of a toxicity table should be made in conjunction with NIAID).

For events not included in the protocol defined grading system, include guidelines here for assessment.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of the onset and duration of each episode.

Relationship Assessment

(*Sample Language*)
For all collected AEs, the clinician who examines and evaluates the subject will determine the adverse event's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related:** There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the

trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely:** A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- **Unrelated:** The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Expected Events Related to Disease Process: Expectedness refers to the awareness of adverse events previously observed, not on the basis of what might be anticipated from the pharmacological properties of the study agent.

Provide explicit definitions of the type(s), grade(s), and duration(s) of adverse event(s) that will be considered disease related.

Relationship Assessment of AEs/SAEs to the Study Agent(s)/Intervention(s) should be made by the principal investigator. (NOTE: Relationship assessment is not a factor in determining what is or is not reported in the study.) Adverse events may have their relationship to the Study Agent(s)/Intervention(s) assessed using the following terms: "associated" or "not associated". Changes in the assessment of relationship to the Study Agent(s)/Interventions should also be clearly documented.

10.4.2 Recording/Documentation

(*Sample Language*)

At each contact with the subject, information regarding adverse events will be elicited by appropriate questioning and examinations and will be immediately recorded on a source document. Source documents will include: progress notes, laboratory reports, consult notes, phone call summaries, survey tools and data collection tools. Source documents will be reviewed in a timely manner by the research team. All reportable adverse events that are identified will be recorded on an appropriate case report form (CRF). The start date, the stop date, the severity of each reportable event, and the PI's judgment of the AEs relationship to the study agent/intervention will also be recorded on the CRF.

The documentation system for the protocol (CRFs, electronic data capture systems, etc) should be clearly described in this section.

Complete description of all adverse events must be available in the source documents. All Adverse Events including local and systemic reactions not meeting the criteria for

"serious adverse events" should be captured on the appropriate case report form or electronic data system. Information to be recorded, based on above assessment criteria, includes event description, time of onset, investigator assessment of severity, relationship to Study Agent(s)/Intervention(s), and time of resolution/stabilization of the event. All adverse events occurring while on study must be documented appropriately regardless of relationship. Define a timeframe for CRF completion and entry of the adverse event information into the database, as applicable.

Any pre-existing medical condition that is present prior to the time that the patient signs initial consent should be considered as baseline and not recorded as an AE. However, if the medical condition deteriorates at any time during the study, it should be recorded and reported as an AE.

10.4.3 Analysis/Management

Describe the provisions for ensuring necessary medical or professional intervention for adverse events of the research. Include the plan to follow all adverse events to adequate resolution. Include plans and procedures, and the persons responsible, for communicating to subjects information arising from the study (on harm or benefit, for example), or from other research on the same topic that could affect subjects' willingness to continue in the study.

10.5 Reporting Procedures

(*Sample Language*)

Adverse event reporting requirements to the NIAID Institutional Review Board (IRB) for this protocol are as follows:

- Investigators will submit a completed serious adverse event report to the NIAID IRB within 7 days after becoming aware of a subject death, a potentially life-threatening (grade 4) serious adverse event that is possibly, probably or definitely related to investigational agent, an urgent inpatient hospitalization or transfer to the ICU.
- Investigators will submit a completed serious adverse event report to the NIAID IRB within 15 days after becoming aware of any Grade 3 (severe) adverse event that is possibly, probably or definitely related to investigational agent, or an inpatient hospitalization (other than elective), a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
- Investigators will report within 15 days on any other event or condition regardless of grade, which in their judgment represents an event reportable to the IRB.
- Investigators will forward all IND safety reports and related FDA communications to the IRB within 15 days of receipt.
- A summary of all adverse events will be reported to the NIAID IRB with a continuing review submission.

(Additional sample language for protocols involving an IDE)

Investigators will submit a report of any unanticipated adverse device effect (UADE) occurring during an investigation as soon as possible but no later than 10 working days after investigator awareness.

This language should be used only if the protocol involves an Investigational Device and is based on FDA regulation 21 CFR 812.150(a)(1).

All clinical trials must have an AE/SAE reporting system in place.

Include details of the protocol-specific reporting procedures, the responsible individuals (e.g., the Investigator, the Medical Monitor, etc.), which case report forms should be completed, how and to whom (IRB, sponsor, DSMB etc) reports will be distributed, and what follow-up is required. The specified time frames for reporting events should be in accordance with applicable regulations, NIAID requirements, any additional institutional requirements and in some cases, specific protocol requirements due to the unique nature of the study.

Include specific details of reporting procedures for:

- *Adverse Events (AEs)*
- *Serious Adverse Events (SAEs) Grade 1-3*
- *Serious Adverse Events (SAEs): Grade 4 or higher*
- *Specify events that require reporting in an expedited time frame (e.g., abnormal laboratory values [Grade 3 or 4], HIV infection, pregnancy) to IND sponsor or other required entities.*
- *Social harms should they be likely to occur in the study on the basis of the study population, intervention, or as a result of the study participation.*

10.5.1 Specific Serious Adverse Event Requirements

All serious adverse events will be:

- *Recorded on the appropriate serious adverse event case report form*
- *Reviewed by a study physician*
- *Followed through resolution by a study physician*

NIAID IRB Reporting Requirements

*Any AE that meets the protocol-specific serious (or expedited) adverse event reporting criteria must be submitted to the NIAID IRB. The following is the **MINIMAL** standard for reporting to the IRB (make specific modifications based on the nature of the individual protocol). The study clinician will complete a Serious Adverse Event Form*

(this form may be found on the NIAID DCR IRB portal/IRB Submission Forms/Serious Adverse Events), within the following timelines:

1) *All deaths: written notification to the IRB within 7 days*
2) *Serious AND unexpected adverse events (this includes all urgent hospitalizations/transfers to ICU):*
    a) *life-threatening-written notification to the IRB within 7 days*
    b) *non life-threatening- written notification to the IRB within 15 days*
3) *All other serious adverse events: at the time of the annual review*

Sponsor Reporting Requirements

If the IND is held by RCHSPB, report serious adverse events to NIAID's pharmacovigilance contractor at the following address, using the appropriate form (if applicable)see reporting information below. Otherwise enter the Sponsor information including the address.

Describe how adverse events, reportable to the IND sponsor, will be followed until resolved or considered stable. Specify procedures for reporting and follow-up of AEs that are consistent with the Schedule of Procedures/Evaluations. Include duration of follow-up period after the appearance of AEs (e.g., one week, two months).

Regulatory Reporting for Studies Conducted Under NIAID-Sponsored IND

(*Sample Language*)

The Regulatory Compliance and Human Subjects Protection Branch (RCHSPB), National Institute of Allergy and Infectious Diseases (NIAID), of the National Institutes of Health (NIH) is the sponsor for the Investigational New Drug application (IND) filed at the U.S. Food and Drug Administration (FDA). In the interest of subject safety in RCHSPB studies and to fulfill regulatory requirements, all deaths and life-threatening SAEs due to any cause, which occur during the course of the study must be reported to the Regulatory Compliance and Human Subjects Protection Program (RCHSPP) Clinical Safety Office within 1 business day after the clinical site becomes aware of the event, and all other SAEs must be reported as soon as possible, but no later than 3 business days.

Serious adverse events will be reported to:

Regulatory Compliance & Human Subjects Protection Program (RCHSPP)
Clinical Safety Office

Phone: 301-846-5301

Fax: 301-846-6224

E-mail: rchspsafety@mail.nih.gov

In accordance with the FDA Code of Federal Regulations (CFR), the IND sponsor RCHSPB must report SAEs that are serious, unexpected, and related to the study intervention to the FDA in the form of a written IND Safety Report.

Deaths and life-threatening events with any possible relationship to a study intervention must be reported to the FDA by telephone or fax as soon as possible but within 7 calendar days of RCHSPB's awareness. This initial report must be followed by as complete a written report as possible within 8 additional calendar days. All other IND Safety Reports must be submitted to the FDA as soon as possible, but no later than 15 calendar days after RCHSPB is notified of the SAE.

SAEs that do not meet the requirements for expedited reporting and all documented adverse events will be reported to the FDA in the IND annual report.

The FDA also requires sponsors to submit a written Safety Report of all serious and unexpected adverse events to all participating investigators of a trial. All participating investigators, at all sites, will be notified of any unexpected SAEs, occurring at other sites, in an IND Safety Report from RCHSPB. RCHSPB will also notify investigators of any revisions to the protocol or to the consent, or study closure. The study investigators in this study have the responsibility of promptly reporting all SAEs so that RCHSPB can comply with these regulations.

Questions about expedited (SAE) SAE reporting can be referred to the Expedited/SAE Hotline (available 24 hours a day/7 days a week).

Contact the NIAID Division or Branch for details on Expedited Adverse Event or SAE reporting.

The study clinician will complete an Expedited or Serious Adverse Event Form located on the NIAID DCR IRB portal/ Serious Adverse Events/ NIAID Reporting Form, within the following timelines:

- *In the interest of subject safety in RCHSPB studies and to fulfill regulatory requirements, all deaths and life-threatening SAEs due to any cause, which occur during the course of the study must be reported to the Regulatory Compliance and Human Subjects Protection Program (RCHSPP) Clinical Safety Office within 1 business day after the clinical site becomes aware of the event, and all other SAEs must be reported as soon as possible, but no later than 3 business days.*
- *Other supporting documentation of the event may be requested by the pharmacovigilance contractor and should be provided as soon as possible.*
- *All reportable AEs will be followed until satisfactory resolution or until the Principal Investigator or Subinvestigator deems the event to be chronic or the participant to be stable.*

Following notification from the investigator, NIAID, the IND sponsor, will report events that are both serious and unexpected and that are associated with Study Agent(s)/Intervention(s) to the FDA and other applicable health authorities within the required timelines as specified in 21 CFR 312.32: fatal and life threatening events within 7 calendar days (by phone /fax/electronic communication) and all other serious adverse events in writing within 15 calendar days. All serious events designed as "not associated" to Study Agent(s)/Intervention(s), will be reported to the FDA at least annually in a summary format. For more information see the SAE flowchart located on the RCHSPB portal/Safety Office (SAE Reporting)/Attachments/SAE Report Flowchart.

10.6 Reporting of Pregnancy

State the study's pregnancy-related policy and procedure. Include appropriate mechanisms for reporting to sponsor, study leadership, IRB, and regulatory agencies. Provide appropriate modifications to study procedures (e.g., discontinuation of Study Agent(s)/Intervention(s) while continuing safety follow-up, following pregnant women to pregnancy outcome). If there are complications during the pregnancy, the complications are recorded as adverse events in the usual way. The participant is asked to report outcome of the pregnancy. If there is a congenital anomaly in the infant, this is recorded as a serious adverse event (SAE) in the data forms for the mother (i.e., the study participant). Also consider language if a woman becomes pregnant while on study and is able to continue receiving the study agent/intervention.

The following is a scenario to consider in the event of pregnancy while on study:

> *Pregnant women are not eligible to participate in the study. Women are counseled regarding prevention of pregnancy and encouraged to make every effort to avoid pregnancy during study participation. If a study participant becomes pregnant during study participation, [are further doses of study agent(s) given or is the study intervention discontinued?]. Depending upon the nature of the study, the pregnancy itself may not need to be recorded as an adverse event. The basic information about the pregnancy is recorded on the "Pregnancy" case report form. Type and Duration of the Follow-up of Participants after Adverse Events*

10.7 Type and Duration of the Follow-up of Participants after Adverse Events

Monitoring of Subjects

(*Sample Language)*

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. AEs may be observed by the Investigator and/or study staff, elicited from the subject and/or family member, reported on subject diary cards [*if applicable*], or volunteered by the study subject. Adverse events that had previously been reported by study subject will also be reassessed for duration, intensity and possible reoccurrence. Assessment of safety will include clinical observation and monitoring of hematological, chemical, and immunologic parameters [*modify as appropriate*].

Address the frequency at which the subjects' disease/condition will be monitored in this research study and compare to the frequency of monitoring associated with standard care for this disease/condition.

(*Sample Language)*

Any AE that occurs between the times a study participant signs the initial informed consent form and the time s/he departs the study at the end of the final follow-up visit (or at the time of early discontinuation of the subject from the study for any reason) will be captured and recorded.

Note that the participant will continue to be followed with the participant's permission, if Study Agent(s)/Intervention(s) is discontinued. Discuss resulting modifications to the schedule and duration of continued follow-up. Adverse event reporting continues for any participant who discontinues the study agent/intervention but continues to be followed on study.

Follow-up of participants after Adverse Events

(*Sample Language)*

All SAEs and non-serious AEs reported in this study will be followed until resolution or until the investigator and the clinical/medical monitor are in agreement that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the patient discontinues participation from the study. These events will be reported to the FDA annually.

(*Additional Sample Language as appropriate)*

Primary care of the patient's initial medical condition will continue to be under the auspices of their local medical provider. A letter describing the study will be sent to the subject's primary care physician. The local medical provider will be instructed verbally and with written guidelines to contact the NIH investigators immediately for any adverse event. A toll-free number will be available to provide 24-hour access to the Principal Investigator or designee. The patient's primary care provider(s) will be encouraged to call the PI should any change in condition be noted as compared to the subject's baseline status. Should the occasion arise, subjects may also be treated at the NIH Clinical Center.

Describe how adverse events will be followed until resolved or considered stable. Specify procedures for reporting and follow-up of AEs that are consistent with the Schedule of Procedures/Evaluations. Include duration of follow-up period after the appearance of AEs (e.g., one week, two months). Include the plan to follow all adverse events to adequate resolution. Include plans and procedures, and the persons responsible, for communicating to subjects information arising from the study (on harm or benefit, for example), or from other research on the same topic that could affect subjects' willingness to continue in the study.

10.8 Modification of Study Agent(s)/Intervention(s) for a Participant

Note: Different types of products will require different instructions for this section. If the study utilizes multiple study agents, clearly indicate toxicity management for each study agent.

*Below is an **example process flow** to describe toxicity for a commonly occurring toxicity related to liver function tests. This type of diagram can be adapted to describe various steps of toxicity management.*

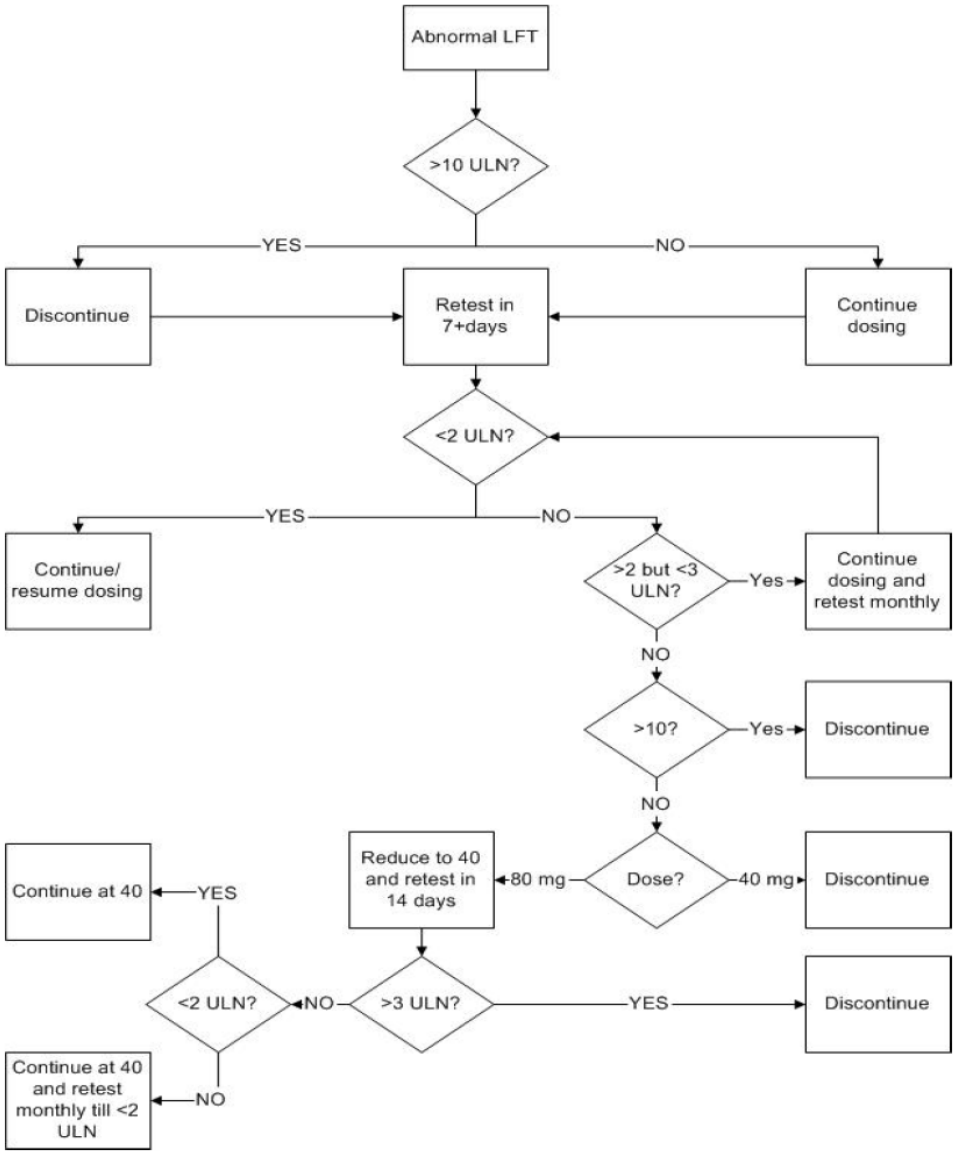


Figure 1:[Liver function test monitoring]

10.8.1 Dose / Schedule Modifications for a Participant

Clearly explain instructions for modification of dose due to toxicity or any other potential reason. Address dose modifications for specific abnormal laboratory values of concern or other adverse events that are known to be associated with the planned intervention regimen.

10.9 Halting Rules for the Protocol

(*Sample Language)*

The Principal Investigator will closely monitor and analyze study data as it becomes available and will make determinations regarding the presence and grading of adverse events. Evaluation of adverse events will be analyzed

separately for [study agent] and [active control] and with regard to the known complications associated with [active control] administration. The study will be halted (no new enrollments and no further [administration of agent/vaccinations]) by the investigators and a report will be submitted to the IRB.

(Include the following language, with appropriate modifications)
The IRB, the NIAID, the pharmaceutical supporter(s), the FDA, or other government agencies, as part of their duties to ensure that research subjects are protected; may discontinue the study at any time. Subsequent review of serious, unexpected and related adverse events by the Medical Monitor, DSMB, ethics review committee or IRB, the sponsor(s), the FDA, and other regulatory authorities may also result in suspension of further trial interventions/administration of study agent at a site. The FDA, other regulatory authorities, and the study sponsor(s) retain the authority to suspend additional enrollment and Study Agent(s)/Intervention(s) administration for the entire study as applicable

Define stopping points and criteria for terminating the study itself. Describe safety findings (e.g., development of a pre-defined number of laboratory toxicities, development of significant AEs in a pre-defined number of subjects, etc.) that would temporarily suspend enrollment and/or study agent/ intervention(s) until a safety review is convened (either routine or ad hoc). The objective of which is a decision as to whether the study agent/intervention (for an individual or study cohort) should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed. Suspension of enrollment (for a particular group or for the entire study) is another potential outcome of a safety review. Include specifics on whom (e.g. safety team, DSMB, or FDA) reviews the data related to the halt and decides if the halt can be ended or must continue.

Examples of findings that might trigger a safety review are: the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

10.10 Stopping Rules for an Individual Participant/Cohort

(*Sample Language)*

A study participant will be discontinued from further [Study Agent/Intervention] administration for:

- Any clinical adverse event, laboratory abnormality, intercurrent illness, other medical condition or situation, such that continued participation in the study would not be in the best interest of the participant.
- Development of any exclusion criteria may be cause for discontinuation.

State the criteria for discontinuation of study agent(s)/intervention(s) for withdrawal of a participant (or a cohort)

In the event that the subject is withdrawn from the study due to an AE, it must be recorded on the CRF as such. The subject should be followed and treated by the

investigator until the abnormal parameter or symptom has resolved or stabilized. It is up to the clinician to determine that the AE is either resolved or that it has reached a stable state, after which no further follow-up is necessary. There should also be documentation to support this determination.

Note that adverse event reporting continues for any participant who discontinues the study agent/intervention but continues to be followed on study.

List possible reasons for discontinuation of the study agent(s)/intervention(s) (for an individual/cohort) in this section, e.g., development of laboratory toxicities, study closure due to DSMB review, discretion of IND holder.

It may be appropriate to provide distinct discontinuation criteria for participants and cohorts. If so, both sets of criteria should be listed separately and the distinction between the two must be stated clearly.

10.11 Premature Withdrawal of a Participant

Describe the follow-up for subjects withdrawn from study; include the type and timing of the data to be collected for withdrawn subjects. The protocol should clearly state that voluntary withdrawal is always an option.

Criteria for Discontinuation or Withdrawal of a Subject: Define stop points and criteria for withdrawing subjects (i.e., "off-study criteria") from the study. If a participant develops an additional condition such as pregnancy, needs surgery, or needs to be hospitalized, the protocol may require withdrawal from a particular study, although not necessarily from others. In studies done with therapeutic intent, the protocol should clarify what the off-study criteria are for "deterioration" or "inadequate control." The wording of this section should clarify the difference between discontinuation of the study drug/intervention and discontinuation of the study (follow-up completed). The protocol should also clearly state that voluntary withdrawal by the participant from the protocol is always an option, and the Principal Investigator may end participation of a subject based on clinical judgment.

10.12 Replacement of a Participant Who Discontinues Study Treatment

Describe whether and how subjects are to be replaced.

11 Clinical Monitoring Structure

This section will describe the study monitoring to be conducted to ensure the safety and conduct of the study complies with 45 CFR 46, GCP and ICH Guidelines, NIAID and other sponsor collaborator's guidelines, as appropriate.

11.1 Site Monitoring Plan

Site monitoring for safety is conducted to ensure the human subject protection, study procedures, laboratory, study agent/intervention(s) administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines.

This section will describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. If the study is monitored by RCHSPB, state that monitoring will be conducted according to the "NIAID Intramural Clinical Monitoring Guidelines." Reference: http://intramural.niaid.nih.gov/ocr/rchspb/NIAIDINTRAMURALDecemberedi.pdf

11.2 Safety Monitoring Plan

The NIAID scientific review committee and the investigators will jointly decide on a safety monitoring plan for each trial. When potential risk to participants is more than minimal, NIAID strongly recommends independent safety monitoring for clinical trials of investigational drugs, devices, or biologics. Phase IV clinical trials of licensed products, and clinical research of any type involving more than minimal risk to volunteers must also have a safety monitoring plan. Independent safety monitoring can take a variety of forms; phase II, III, and IV clinical trials generally require an independent Data and Safety Monitoring Board (DSMB). NIH policy for data and safety monitoring boards may be found at the following internet web address: http://grants.nih.gov/grants/guide/notice-files/not98-084.html and http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html. NIH policy requires each IC to oversee and monitor clinical trials; some monitoring requirements may vary by NIAID division.

At this time, the following types of NIAID Intramural Program protocols will be monitored by RCHSPP or another independent monitoring group:

- *RCHSPB-held IND studies;*
- *International protocols funded by NIAID or with a NIAID PI, listed as the Principal Investigator;*
- *Protocols enrolling pediatric subjects or other vulnerable populations;*
- *Special requests from the Clinical Director;*
- *At the request of the Principal Investigator.*

11.2.1 Safety Review Plan by the DSMB / SMC/ Medical Monitor

Provide the method and frequency of the safety review plan, if applicable. See below for the function of SMC/DSMBs:

- ***Safety Monitoring Committee (SMC):** is an independent group of experts that advises the study investigators for Phase I and some Phase II trials. The primary responsibility of the SMC is to monitor participant safety. The SMC considers study-specific data as well as relevant background information about the disease, test agent, and target population under study. To learn more about the role and function of SMCs read, http://www.niaid.nih.gov/dmid/clinresearch/smc.htm.*
- ***Data and Safety Monitoring Board (DSMB):** is an independent group of experts that advises the study investigators.. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make*

recommendations concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. To learn more about the role and function of DSMBs read, the NIAID DSMB Policy and SOP, both of which are located on the NIAID DCR IRB portal/Clinical Research Guidance/Guidance for Investigators and the DSMB Guide for Investigators located on the RCHSPB portal/Data Safety and Monitoring Board (DSMB)/Attachments/DSMB Guide for Investigators.

For example, a DSMB may be convened if a study meets one or more of the following criteria:

- *Will generate randomized, blinded data,*
- *Is a multi-center protocol which presents more than minimal risk to subjects;*
- *Uses gene transfer or gene therapy methodology;*
- *Requires special scrutiny because of high public interest or public perception of risk;*
- *NIAID policy mandates that it be reviewed by the NIAID Intramural Data and Safety Monitoring Board (DSMB).*

- ***Medical Monitor:*** *is an independent medical expert that advises the study investigators and monitors participant safety. A study may choose to employ the services of, or may be appointed a Medical Monitor. The role of the Medical Monitor is to:*

    1) *Review all adverse events (AEs) on a regular basis throughout the trial;*
    2) *Be available to advise the investigators on trial-related medical questions or problems,*
    3) *Evaluate cumulative subject safety data and make recommendations regarding the safe continuation of the study.*

  The Medical Monitor will remain blinded throughout the conduct of the clinical trial unless unblinding is warranted to optimize management of an adverse event or for other safety reasons.

(Sample Language, if NIAID DSMB Monitored protocol)

The NIAID Intramural DSMB will review the IRB approved protocol, informed consent documents, the data and safety monitoring plan and any stopping guidelines prior to study initiation, unless otherwise waived by the NIAID Clinical Director. During the course of the study, the DSMB will review cumulative study data twice per year [*Edit as appropriate per protocol- e.g., before dose escalation as well as twice per year*] to evaluate safety, efficacy, study conduct, and scientific validity and integrity of the trial. As part of this responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the safety and welfare of study subjects. The DSMB may also convene as needed if stopping criteria are met or other safety issues arise that the Principal Investigator and/or NIAID Clinical Director or designee would like the DSMB to address.

The protocol-specific statistician or other appropriate individual will provide the DSMB Executive Secretary with up to date blinding codes in a sealed envelope in the event that the DSMB will require this information to make its recommendations. The Principal Investigator will notify the DSMB of all cases of unblinding, intentional or unintentional, so that the DSMB can assess the potential impact of the unblinding on the overall integrity of the study. *[Delete paragraph if study is not blinded]*

The Principal Investigator will submit the written DSMB recommendations to the IRB upon receipt.

12 Statistical Considerations

This section should describe the statistical tests and analysis plans for the protocol.

In the introductory section provide an overview of the restate the scientific rationale for the study and the primary and most important secondary objectives from Section 3, to motivate choice of study population, outcome measures, hypotheses and design, as related to the statistical analysis plan for this protocol.

Describe cohorts including control groups (i.e., active or placebo control groups, concurrent or historical controls, etc.) and a synopsis of the rationale for choosing them (i.e., including risk/benefit or other ethical factors).

12.1 Overview and Study Objectives

Succinctly restate the scientific rationale for the study and the primary and most important secondary objectives from Section 3, to motivate choice of study population, outcome measures, hypotheses and design.

12.2 Study Population

Give a very concise restatement of the eligibility criteria, e.g., vaccinia-naïve healthy volunteers between the ages of 18 and 65.

Describe any control groups (i.e., active or placebo control groups, concurrent or historical controls, etc.) and a synopsis of the rationale for choosing them (i.e., including risk/benefit or other ethical factors).

12.3 Description of the Analyses

State the proposed formal design of the study (e.g., two-period crossover, two-by-three factorial parallel group, or case-control). If the design or interventions are complex, a schema may be included.

12.4 Measures to Minimize Bias

Enrollment/ Randomization/ Masking Procedures

This section contains a description of enrollment procedures and randomization (if applicable to the study design) and masking procedures. It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that masking or randomization might be compromised (e.g., the ratio between intervention and placebo groups may be stated but the randomization block sizes should not). A discussion of the impact of replacement of participants who discontinue early, if allowed, on the statistical analysis/power calculations.

Plans for the maintenance of trial randomization codes and maintaining appropriate masking for the study should be discussed. The timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unmasking may occur and who may unmask.

Review strategies to avoid bias, such as randomization and masking methods, or decrease variability, such as centralized laboratory assessments. DO NOT include details that might compromise these strategies, such as the size of randomized blocks.

Masking/Blinding Procedures: A description of the specific procedures to be used to carry out blinding should be provided (e.g., how bottles to be labeled, use of labels that reveal blind-breakage, sealed code list/envelopes, double dummy techniques).

- *Establishment of Subjects Codes*
- *Storage/Location of Subject Identification Codes*

Maintenance of Blind: If the study allows for some investigators to remain unblinded (e.g., to allow them to adjust medication), the means of shielding other investigators should be explained. Measures taken to ensure that test drug/investigational product and placebo are indistinguishable and evidence that they are indistinguishable should be described, as should the appearance, shape, smell, and taste of the test material. Measures to prevent unblinding by laboratory measurements, if used, should be described.

Evaluation of Success of Blinding

Provide the criteria for determining the success of blinding.

Breaking the Study Blind/ Subject Code.

Criteria for Breaking the Study Blind/Subject Codes: Discussion of the circumstances in which the blind would be broken for an individual or for all patients (e.g., for serious adverse events).

Procedures for Breaking the Study Blind/ Subject Code.

If blinding is considered unnecessary to reduce bias for some or all of the observations, this should be explained; e.g., use of a random-zero sphygmomanometer eliminates possible observer bias in reading blood pressure and Holter tapes are often read by automated systems that are presumably immune to observer bias. If blinding is considered desirable but not feasible, the reasons and implications should be discussed. Sometimes blinding is attempted but is known to be imperfect because of obvious drug

effects in at least some patients (dry mouth, bradycardia, fever, injection site reactions, changes in laboratory data). Such problems or potential problems should be identified and, if there will be any attempts to assess the magnitude of the problem or manage it (e.g., by having endpoint measurements carried out by people shielded from information that might reveal treatment assignment).

12.5 Appropriate Methods and Timing for Analyzing Outcome Measures.

An outcome measure is "an observation variable recorded for [participants] in the trial at one or more time points after enrollment for the purpose of assessing the effects of the study treatments"(Meinert 1986). Outcome measures should be prioritized. Generally, there should be just one primary variable, with evidence that it will provide a clinically relevant, valid and reliable measure of the primary objective (e.g., laboratory procedures, safety assays).

Give succinct but precise definitions of the outcome measures used to measure the primary and key secondary outcomes stated in the study objectives, including the study visits at which the samples will be obtained and the specific laboratory tests to be used.

Secondary outcome measures should be included, whether they add information about the primary objective or address secondary objectives. Discuss their importance and role in the analysis and interpretation of study results.

Discuss how the outcome measures will be measured and transformed, if relevant, before analysis (e.g., Is the primary variable binary, categorical, or continuous? Will a series of measurements within a participant be summarized, such as by calculating the area under the curve? For survival outcome measures, what are the competing risks and censoring variables?).

12.6 Study Hypotheses

Provide all information needed to validate your calculations, and also to judge the feasibility of enrolling and following the necessary numbers of participants.

In particular, specify all of the following:

- *Outcome measure used for calculations (almost always the primary variable)*
- *Test statistic*
- *Null and alternate hypotheses*
- *Type I error rate*
- *Type II error rate*
- *Assumed event rate for dichotomous outcome (or mean or variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible*

- *Assumed rates of drop-out, withdrawal, cross-over to other study arms, missing data, etc. also justified*
- *Approach to handling withdrawals and protocol violations, i.e., whether "intent to treat"*
- *Statistical method used to calculate the sample size, with a reference for it and for any software utilized*
- *Method for adjusting calculations for planned interim analyses, if any*
- *Present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size.*

Discuss whether the sample size also provides sufficient power for addressing secondary objectives, or for secondary analyses in key subgroup populations.

12.7 Sample Size Consideration

Provide all information needed to validate your calculations, and also to judge the feasibility of enrolling and following the necessary numbers of participants.

In particular, specify all of the following:

- *Outcome measure used for calculations (almost always the primary variable)*
- *Test statistic*
- *Null and alternate hypotheses*
- *Type I error rate*
- *Type II error rate*
- *Assumed event rate for dichotomous outcome (or mean or variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible*
- *Assumed rates of drop-out, withdrawal, cross-over to other study arms, missing data, etc. also justified*
- *Approach to handling withdrawals and protocol violations, i.e., whether "intent to treat"*
- *Statistical method used to calculate the sample size, with a reference for it and for any software utilized*
- *Method for adjusting calculations for planned interim analyses, if any*
- *Present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size.*

Discuss whether the sample size also provides sufficient power for addressing secondary objectives, or for secondary analyses in key subgroup populations.

12.8 Maintenance of Trial Treatment Randomization Codes

(*Sample Language)*

The randomization sequence will be obtained by computer-generated random numbers and provided to the pharmacist by the statistician. The subject, the clinical staff, and the Principal Investigator will be blinded to treatment allocation. The pharmacist with primary responsibility for drug dispensing will keep the randomization code.

Randomization Process: Describe the registration process to the protocol and include procedure for Data Management Center randomization, steps, and/or means for assigning subjects to therapies. Discuss method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned. Discuss who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.

12.9 Participant Enrollment and Follow-Up

Summarize the total number of enrolled participants and the total duration of accrual and of final follow-up.

Be specific about the number of clinical sites and the expected recruitment and retention capabilities of each site. Be explicit about distinct stages in enrollment, if applicable.

Identify strategies for subject retention. Discuss plans for maintaining the cooperation of the study population as well as plans for addressing any anticipated changes in the composition of the study population over the course of the trial. Data should be presented supporting recruitment retention estimates.

12.10 Planned Interim Analyses

If interim analyses will be reviewed by Data and Safety Monitoring Board (DSMB) or a similar committee, (SMC), describe the frequency of review (e.g., on a quarterly basis).

Describe the types of statistical interim analyses and stopping guidelines (if any) that are proposed, including their timing.

Within the two sections below, the criteria used to determine decisions should be pre-specified to the extent possible.

12.11 Safety Review

Provide details of the proposed rules for halting study enrollment or study agent/intervention(s) administration of study product for safety, including whether they pertain to the entire study, specific study arms or participant subgroups, or other components of the study.

State the safety outcome measures that will be monitored, the frequency of monitoring, and the specific definitions of proposed stopping guidelines.

If statistical rules will be used to halt enrollment into all or a portion of the study, describe the statistical techniques and their operating characteristics, e.g., the probability of stopping under different safety event rates and the associated number of participants that would be enrolled.

12.12 Immunogenicity or Efficacy Review

Provide the information for immunogenicity or efficacy outcome measures. Also discuss the impact of the interim monitoring plan on final efficacy analyses, particularly on Type I error.

If formal interim analyses will be performed, provide unambiguous and complete instructions so that an independent statistician could perform the analyses.

12.13 Final Analysis Plan

This section can be used to elaborate on primary analyses that underlie the sample size calculation and to describe secondary analyses for the primary or secondary objectives. Even more details can be provided in a separate statistical analysis plan written later, but prior to performing any analyses.

Plans must clearly identify the analyses cohorts (e.g., "Per Protocol" or "Intent to Treat", as well as subsets of interest) and methods to account for missing, unused or spurious data.

The main aim of the description of the statistical analyses is to convince the reviewer that the researcher has the ability to undertake appropriate analyses that answer the research objectives. State the primary and null hypotheses and discuss other secondary/tertiary hypotheses.

- General Design: *Discuss choice of study design (e.g., parallel groups, crossover, immediate versus deferred intervention, factorial, large simple trial, equivalency or non-inferiority trial). Discuss why certain design features were chosen (e.g., for a crossover trial, how the length of the washout period was chosen). Describe the parametric or non-parametric statistical methods/tests to be used, also the desired significance level or confidence interval. Justify the use of a non-parametric method, if applicable.*
- Study Endpoints: *The endpoints of the study are the overall outcomes that the protocol is designed to evaluate.:*
    - Primary:
        - Definition: *Define the primary outcome of interest and how that relates to the objectives.*
        - Validity and Reliability: *Discuss methods used to improve the quality of measurements, such as multiple observations. Indicate the "promising" range, the range of true values sufficiently promising to justify further testing of the agent (e.g., true response rate of at least 40%). Likewise, for the primary endpoint indicate the "discouraging" range -- that is, a range of values sufficiently discouraging to justify no further testing of the agent (e.g., true response rate no greater than 20%). Give the probability of a positive result, given that the true value falls within the promising*

range, and the probability of a negative result (along with the probability of early negative termination), given that the true value falls within the discouraging range. The ranges of promising values and discouraging values should reflect results from the single agents (or from partial combinations, if more than two agents are combined in the current regimen). These results should be referenced.

- Secondary:
  - Definition: *In particular, brief descriptions should be given of pharmacokinetic, biologic, and correlative laboratory endpoints.*
  - Validity and Reliability: *Specify how they will be analyzed.*

- Description of the Statistical Methods to Be Employed: *The ability to detect a clinically relevant effect, or power, can be augmented by determining the correct design and correct sample size for the study and by carefully considering the principal end point of interest, the magnitude of effects that would be of clinical importance, and the acceptable probabilities of making an error. If specialized statistical techniques (e.g., methods for sequencing or microarray analysis) will be used, discuss and indicate who will be performing the analysis.*
- Level of Significance to be Used*: The way in which statistical significance is determined depends on the design of the trial and the manner in which the trial questions are specified. Statistical significance can be achieved only if the size of the sample is adequate for identifying an effect of the magnitude that is of interest. Also, statistical significance at a particular level is more likely to be observed if accumulated study data are repeatedly tested for significance. If repeated evaluation is planned, it should be specified in the protocol.*
- Accrual and Sample Size Considerations: *Give the rationale for the proposed sample size. Present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size. Discuss whether the sample size also provides sufficient power for addressing secondary objectives, or for secondary analyses in key subgroup populations. To determine the sample size, select the maximum probability of errors (or statistical power) that can be made. It is reasonable and customary to allow a maximum type I error probability of no greater than 5% and a maximum type II error probability of no greater than 20%, or else 10% for each type of error.*
- Relationship(s) of Endpoints to Calculations: *Determining the size of the sample depends on the nature of the end points. The objective should have one clearly definable, readily quantified end point. To compare differences in quantities, identify how large a difference is of interest if a difference rarely exists between the interventions being compared. To identify reasonable differences in interventions, review existing literature on the treatments to obtain the best estimates for the patient population. Decide if the difference between groups is to be evaluated by a one-sided or a two-sided hypothesis test. The standard approach in many fields is to select a two-sided hypothesis test in order to allow for the possibility that observed differences, if any, may be opposite to those expected.*
- Analysis Plan: *Outline how data will be transformed and analyzed. If the analysis involves paired or repeated measurement data, describe the appropriate methods. If necessary, provide details to check assumptions required for certain types of data,*

e.g., proportional hazards, normality, etc. Describe whether multivariate analysis will be used for prediction or for controlling extraneous variables in a hypothesis test. If regression methods will be used, describe how the parsimonious model will be selected. If appropriate, describe how the final model will be interpreted.

- Analysis of Variables: *Indicate independent and dependent variables. Outline how these important variables will be analyzed. Variables may be classified as nominal, ordinal, or interval. These three types of classifications are sometimes overlapped.*
- Baseline Comparability: *Groups should be compared for baseline characteristics including demographics and laboratory measurements, using descriptive statistics.*
- Safety Analysis: *The primary measure of safety of the study agent should be defined. It is not intended that every adverse event be subjected to rigorous statistical evaluation.*
- Efficacy Analysis: *The primary measure of efficacy should be defined. Details of the statistical analysis to be performed on each primary efficacy variable should be provided.. Discuss whether the analysis will be by "intention to treat" with another analysis for evaluable patients only. However, an analysis based on a subset of patients must explain which patients to be excluded and for which reasons. If there is more than one primary endpoint (outcome variable) or more than one analysis of a particular endpoint the statistical analysis should reflect awareness of this and either explain the statistical adjustment used for type I error criteria or give reasons why it was considered unnecessary.*
- Subpopulation Analyses of Intervention Effect: *In accordance with NIH policy, if data from prior studies do not negate strongly the existence of significant differences of clinical or public health importance in the intervention effect between gender and racial/ethnic subgroups, a statement should be included noting that a valid analysis of the intervention effect will be performed in these subgroups. If data from prior studies do not support strongly the existence of significant differences in the intervention effect between subgroups, then the analyses need not have high statistical power for detecting clinically meaningful differences.*
- Exploratory Analyses: *Exploratory analysis is analysis that is not stated in the original analysis plan. For example an interesting or unanticipated effect or event that warrants a closer analysis of data.*
- Handling of Missing and Spurious Data: *Describe how missing data, outliers, noncompliance and losses to follow-up will be handled in the analyses.*

13 Quality Control and Quality Assurance

(*Sample Language)*

Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

Quality control procedures will be implemented beginning with the data entry system and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Definitions:

- *Quality assurance (QA): the systematic and independent examination of all study-related activities and documents. These audits determine whether the evaluated activities were appropriately conducted and that the data were generated, recorded, analyzed, and accurately reported according to protocol, standard operating procedures (SOPs), and good clinical practices (GCPs). (ICH E6 1.46).*
- *Quality control (QC): periodic operational checks within each functional department to verify that clinical data are generated, collected, handled, analyzed, and reported according to protocol, SOPs, and GCPs. (ICH E6 1.47).*
  Larry.Niemoeller@HHS.GOV

This section will indicate the plans for local quality control (QC). Each site should have standard operating procedures (SOPs) for quality management. Data will be evaluated for compliance with protocol and accuracy in relation to source documents. The study will be conducted in accordance with procedures identified in the protocol. The types of materials to be reviewed, who is responsible, and the schedule for reviews may be specified or referenced in other documents. Types and mechanisms of training of staff for the study should be specified.

Specify whether the study will be conducted at multiple centers or a single center.

SOPs must be used at all clinical and laboratory sites. Regular monitoring and an independent audit must be performed according to ICH-GCP (e.g., data monitoring).

Briefly describe methods (e.g., site monitoring) for assuring protocol compliance, ethical standards, regulatory compliance and data quality.

14 Ethics/Protection of Human Subjects

This section should include a description of the ethical considerations and context for the conduct of the trial.

14.1 The Belmont Report

(*Sample Language)*

In accordance with the FWA00005897: "This institution assures that all of its activities related to human subject research, regardless of funding source, will be guided by the ethical principles of The Belmont Report." Additionally, the investigator assures that all activities of this protocol; will be guided by the ethical principles of The Belmont Report, 45 CFR 46 and all of its subparts (A, B, C and D).

14.2 Declaration of Helsinki

(Sample Language)

The investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki, or with the International Conference for Harmonization Good Clinical Practice (ICH-GCP) regulations and guidelines, whichever affords the greater protection to the subject.

If the study is conducted at international sites, include a statement about compliance with the Declaration of Helsinki.

14.3 Institutional Review Board

(Sample Language)

A copy of the protocol, informed consent forms, other information to be completed by participants, such as survey instruments or questionnaires, and any proposed advertising/ recruitment materials will be submitted to the IRB for written approval.

The investigator must submit and obtain approval from the IRB for all subsequent amendments to the protocol, informed consent documents and other study documentation referenced above. The investigator will be responsible for obtaining IRB approval of the annual Continuing Review throughout the duration of the study.

The investigator will notify the IRB of violations from the protocol and serious adverse events.

To review the HHS regulations for the protection of human subjects (45 CFR 46.109) regarding regulations relating to items that require review by the IRB refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.109 .

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate ethics review committee or Institutional Review Board (IRB). Any amendments to the protocol or consent materials must also be approved before they are placed into use.

In both the United States and in other countries, only institutions holding a current U. S. Federal-Wide Assurance issued by the Office for Human Research Protections (OHRP) may participate. For guidance on FWAs, refer to: http://www.hhs.gov/ohrp/assurances/assurances_index.html . To search an institution to see if they have a FWA: http://ohrp.cit.nih.gov/search/asearch.asp#ASUR .

Other items under IRB oversight

All materials utilized for recruitment of participants including advertisements, study websites, pamphlets, and flyers must be reviewed by the IRB. The FDA requires that an Institutional Review Board (IRB) review and have authority to approve, require modifications in, or disapprove all research activities covered by the IRB regulations [21 CFR 56.109(a)]. An IRB is required to ensure that appropriate safeguards exist to protect the rights and welfare of research subjects [21 CFR 56.107(a) and 56.111]. In fulfilling these responsibilities, an IRB is expected to review all the research documents

and activities that bear directly on the rights and welfare of the subjects of proposed research.

Note also that certain activities regarding the disposition and use of stored samples is also subject to IRB oversight, please see protocol Section 8 .

"For studies conducted under an investigational new drug application, an investigator's brochure is usually required by FDA [21 CFR 312.23(a)(5) and 312.55]. Even though 21 CFR part 56 does not mention the investigator's brochure by name, much of the information contained in such brochures is clearly required to be reviewed by the IRB." For more guidance regarding the Investigator Brochure refer to: http://www.fda.gov/oc/ohrt/irbs/default.htm .

14.4 Informed Consent Process

(*Sample Language)*

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the participants and their families. Consent forms describing in detail the study agent/intervention(s) study procedures and risks will be given to the participant and written documentation of informed consent is required prior to starting study agent/intervention. Consent forms will be IRB approved and the participant will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant and answer any questions that may arise. The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The acquisition of informed consent will be documented in the subject's medical records, as required by 21 CFR 312.62. The informed consent form will be signed and personally dated by the subject and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the medical chart and a copy will be provided to the participant.

Describe the procedures for obtaining and documenting informed consent of study participants. Make provisions for special populations, e.g., non-English speakers, children, illiterate or non-writing individuals, vulnerable populations, cognitively impaired subjects

Except as described in 21 CFR 50.23, informed consent is required for all subjects participating in an NIAID-sponsored study. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and

should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator must have the IRB/Independent Ethics Committee's written approval/favorable opinion of the written informed consent form(s) and any other written information to be provided to the participants.

Ethical considerations and Federal regulations (45 CFR 46) [Add 21 CFR 50 for studies under IND] require that investigators obtain the informed consent of the subject or permission from the subject's legally authorized representative as defined in 45CFR.46.102(c) before any research procedures are initiated. Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation.

The consent form shall include all elements required by 45 CFR 46.116 [Add 21 50.25 if under IND] and any other information needed for an individual to be fully informed about study participation. The consent process and document shall not include language waiving or appearing to waive any legal rights of the subject or releasing or appearing to release the investigators, sponsor, or institution from liability.

In certain circumstances (e.g., illiterate research subjects) an IRB approved written summary of what the PI (or person authorized to obtain consent) will say to the subject or his/her legally authorized representative will be presented and signed by the person obtaining consent and an impartial witness to the oral presentation. A short written consent form stating that the required elements of consent as required by 45 CFR 46.116 [Add 21 50.25 if under IND] and NIH Clinical Center policy M77-2-rev, were presented orally to the subject by the PI (or his designate) shall be signed by the subject and an impartial witness who observed the presentation of information. Copies of both documents will be given to subjects or their representatives and filed in the participant's medical record.

If there is a non-English speaking participant, an IRB approved translated consent document shall be presented as per 45 CFR 46.117 (b)(1) and NIH Clinical Center policy M77-2-rev. [ADD per 21 CFR 50.20 if under IND].

In the case of participants who are cognitively impaired or a protocol that will involve participants who are cognitively impaired refer to NIH Clinical Center Policy M87-4. Additionally, it is strongly suggested that you seek consultation with the Department of Clinical Bioethics.

Screening Consent: If screening procedures are required for eligibility (e.g., laboratory tests), there must be a separate screening consent form in addition to the informed consent form for study participation. Specify allowable windows for pre-entry evaluations relative to screening evaluations and study entry.

If a separate screening consent is required for the study, the Screening and the Study consents/assents should be provided to the participant/participant's guardian in sufficient time prior to start of study participation for the participant to fully review, comprehend and discuss the contents. For guidance on informed consent refer to the OHSR Information Sheets/Forms - Sheet 6 GUIDELINES FOR WRITING INFORMED CONSENT DOCUMENTS.

14.4.1 Assent or Informed Consent Process (in Case of a Minor)

Assent: When a prospective subject is not capable of informed consent, this section should discuss satisfactory assurance that permission will be obtained from a duly authorized person, or, in the case of a child who is sufficiently mature to understand the implications of informed consent but has not reached the legal age of consent, that knowing agreement, or assent, will be obtained, as well as the permission of a parent, or a legal guardian or other duly authorized representative.

If a study includes participants who may only be enrolled in the trial, via the permission of the participant's legally acceptable representative (e.g., minors or participants with severe dementia); the study must inform the participants to the greatest extent possible about the trial, consistent with the participant's level of understanding. If capable, the participant should assent and sign and personally date the written consent form. A separate IRB-approved assent form, describing (in simplified, age-appropriate terms) the details of the study agent/intervention(s), study procedures and risks may be used. Assent forms do not substitute for the consent form signed by the participant's legally acceptable representative. Refer to 45 CFR 46.408 for requirements on obtaining consent from Parents and Guardians and obtaining Assent from Children.

14.5 Justification for Exclusion of Women, Minorities, and Children (Special Populations)

If the study intends to exclude any special populations, justify the exclusion of women, minorities or children in the context of the study design. Use this section only if not previously addressed in Section 5.2 – Participant exclusion criteria.

Exclusion of Women: *(if applicable)*

Exclusion of Minorities: *(if applicable) If minorities will not be recruited, explain why not. Provide justification for exclusion in Ethics/Protection of Human Subjects section.*

Exclusion of Children: *(if applicable) If children will not be recruited, explain why not. Provide justification for exclusion in this section. For more information on special protections for children, refer to 45 CFR 46, Subpart D. For more information on NIH policy regarding including children in research refer to the, "NIH POLICY AND GUIDELINES ON THE INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS".*

14.6 Participant Confidentiality

(Sample Language)

The investigator will ensure that the subject's anonymity is maintained. Subjects will not be identified in any publicly released reports of this study. All records will be kept confidential to the extent provided by federal, state and local law. The

study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. The investigator will inform the subjects that the above-named representatives will review their study-related records without violating the confidentiality of the subjects. All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number in order to maintain subject confidentiality. All records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, [the FDA], the NIAID, the OHRP, [the pharmaceutical supporter(s)], or the sponsor's designee.

Include procedures for maintaining participant confidentiality, any special data security requirements, and record retention per the sponsor's requirements.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The Federal Privacy Act protects the confidentiality of study participants' NIH medical records. However, the Act allows release of some information from the medical record without the subjects' permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized persons. To view the amended Federal Privacy Act go to: http://www.usdoj.gov/foia/privstat.htm

14.7 Study Discontinuation

In the event that the study is discontinued, provide a plan for the following:

- *Describe procedures for participants to continue therapy, if appropriate.*
- *Crossover to study agent for placebo recipients at the completion of the study.*

15 Data Handling and Record Keeping

Include instructions for special data handling or record keeping procedures required for maintaining participant confidentiality, any special data security requirements, and record retention per the sponsor's requirements in this section.

Briefly describe steps to be taken to assure that the data collected are accurate, consistent, complete and reliable and in accordance with ICH GCP guidelines. The description should include reference to source documentation, case report forms, instructions for completing forms, data handling procedures, and procedures for data monitoring. Details may be provided in a Manual of Procedures (MOP), User's Guide or other citable reference document.

15.1 Data Management Responsibilities

Describe responsibilities for data handling and record keeping as they specifically relate to the sponsor, clinical site, laboratory, and data coordinating center (if applicable). Information should include who is responsible for data collection, review of data, trial materials, and reports, as well as retention of source documents, files, and records. Describe coding dictionaries to be used and reconciliation processes (if applicable).

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse Events must be graded, assessed for severity and causality and reviewed by the site Principal Investigator or designee.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. During the study, the Investigator must maintain complete and accurate documentation for the study.

If data are to be generated in one location and transferred to another group, describe the responsibilities of each party.

Indicate the roles of each party with regard to interpretation of data, plans for analysis, review of tables and listings, and plans for reporting.

Data Sharing Procedures, if applicable: Describe briefly the expected schedule for data sharing, a brief description of the data sharing agreement (including the criteria for deciding who can receive the data and whether or not any conditions will be placed on their use), and the mode of data sharing (e.g., by mailing a disk or posting data on a website, through a data archive or enclave). Specific issues and opportunities related to sharing resources developed at a foreign site should be mentioned.

If data such as, information, biological materials or laboratory samples will be shared with outside collaborators, you must work with NIAID's Office of Technology Development to determine the proper vehicle for such a collaboration. For the definition of a Materials Transfer Agreement (MTA) or Cooperative Research an Development Agreement (CRADA), go to: http://www3.niaid.nih.gov/about/organization/odoffices/omo/otd/When_to_use_MTA_CRADA.htm . Ask to speak with the DIR Team at 301-496-2644.

15.2 Data Capture Methods

Identification of direct CRF input data and other source data

Provide details regarding the type of data capture that will be used for the study. Specify whether it will be paper or electronic, distributed or central, batched or ongoing processing, and any related requirements

15.3 Types of Data

Indicate the types of data that will be collected, such as safety, laboratory (clinical, immunology, pharmacokinetic, other study specific), and outcome measure data (e.g., reactogenicity). Specify if safety data are collected in a separate database.

15.4 Source documents and Access to Source Data/Documents

(*Sample Language)*

Study data will be collected on case report forms (CRF) designed for the study[, or an electronic data system (CRIMSON)]. The Principal Investigator is responsible for assuring that the data collected is complete, accurate, and recorded in a timely manner. Source documentation (the point of initial recording of a piece of data) should support the data collected on the case report form [or CRIMSON, and in the case of CRFs be signed and dated by the person recording and/or reviewing the data.] Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical trial. Data for CRFs will be collected during patient visits, phone calls with subjects and health care providers, patient diaries and abstracted from the medical record. The CRF form may act as the source document for the following study procedures: [Specific procedures]. It is not acceptable for the CRF to be the only record of a patient's participation in the study. This is to ensure that anyone who would access the patient medical record has adequate knowledge that the patient is participating in a clinical trial.

Appropriate medical and research records for this trial will be maintained in compliance with ICH-GCP, regulatory and institutional requirements for the protection of confidentiality of participants. Describe who will have access to records. Authorized representatives of the sponsor(s), NIAID, and regulatory agencies will be permitted to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

15.5 Timing/Reports

Indicate the schedule for data review and reports, how outcome measure data are collected and monitored, data for stopping rules, and reports for DSMB. Specify whether reviews or reports are ongoing, interim, or periodic. Identify plans for data analysis and interim and final study reports, steps for freezing the data prior to analysis, and precautions related to masked data. Indicate whether and when coding is to occur.

15.6 Study Records Retention

Specify the length of time for the investigator to maintain all records pertaining to this study (e.g., a minimum of two years following the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the Study Agent/Intervention(s). Indicate whether permission is required (and from whom) prior to destruction of records. If the trial is under IND, records should not be destroyed without the IND sponsor's agreement. Pharmaceutical companies who supply unregulated products should be consulted.

The investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice Guideline. All essential documentation for all study subjects are to be maintained by the investigators in a secure storage facility for a minimum of three years, per NIH FWA. [If under IND: The FDA requires study records to be retained for up to two years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication]. These records are also to be maintained in compliance with IRB/EC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent provided by federal, state, and local law.

Study Agent/Intervention(s) records may be addressed here if not addressed elsewhere in the protocol.

16 Publication Policy

(*Sample Language)*

Following completion of the study, the investigator may publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the NIAID Division or Branch to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered either on or before the onset of patient enrollment.

The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or comparison groups to study the

cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase 1 trials), would be exempt from this policy.

Publication of the results of this trial will be governed by NIAID publication policies. Any presentation, abstract, or manuscript will be made available for review (according to division requirements if any), prior to submission. For NIAID pre-publication clearance see "Obtaining Pre-Publication Clearance for Intramural Manuscripts". For more information on the NIH Manuscript Submission System, see the NIH Manuscript Submission Program.

In the case of collaborative studies with co-sponsoring agencies or other clinical trial groups, any letter of agreement must note which Standard Operating Procedure for publication of research findings is used. See Section 15.1 – Data Management Responsibilities for information on obtaining agreements.

Additional Considerations for the above section:
If appropriate, the publication policy may be described in the study Manual of Procedures (MOP). The publication and authorship policies should be determined and clearly outlined in this section. Refer to contract or clinical trials agreements. Policies regarding substudies should be outlined in this section.

Appendices are supplemental material (e.g., flow diagrams or workup tables) or other documents (like the Investigator's Brochure) may be added to the protocol as appendices. Appendices A-C are required or recommended as applicable to the specific study. Remember that modifications to appendices require submission of an amendment to the NIAID IRB as appendices are part of the protocol document.

It is not recommended that the Informed Consent Forms or the List of Persons Able to Obtain Informed Consent be included in the appendices. The Informed Consent form may require more frequent amendments than the remainder of the document and can easily become out-of-sync with the protocol. Note that the List of Persons able to Obtain Informed Consent may be revised and submitted to the NIAID IRB as an Information Item and does not require an Amendment request.

Appendix A: Scientific References

(This section is required)

References enable others to verify assertions in the protocol and to further pursue its topics, particularly the protocol's description of the present state of knowledge, the measures to be used, any risks/discomforts expected, and other points that are attributable to specific sources. Provide citations for publications and presentations referenced in the text of the protocol. For unpublished work, provide names and contact information. Use a consistent, standard, modern format. The preferred format is the Vancouver format, used in the American Medical Association Manual of Style

Access PubMed a service of the NIH National Library of Medicine, providing access to 12 million MEDLINE citations and numerous life science journals as well as links to full text articles. Go to PubMed. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi

Appendix B: Toxicity Table

(This section is required as applicable)

Provide either the actual table or a weblink to the table. Paste the link from the source or Right-click and select "Hyperlink…", then select "Existing File or Webpage", then browse to the desired source, once it is selected, Click "OK".

Appendix C: Schedule of Procedures/Evaluations

(This section is required)
(Sample Language)

Evaluation	Screening (-30 days)	Baseline (-14 days)	Day 0	4	8	12	16	20	24	32	40	48	Prem. Disc. Evals.
Medical/Medication History													
Clinical Assessment													
[Complete/Targeted] Physical Exam													
[Other Clin. Assess. components if on a different schedule]													
Hematology													
PT/PTT													
Chemistry													
Liver Function Tests													
Urinalysis													
Pregnancy Testing													
Chest X ray													
HIV-1 RNA (real time)													

Appendix D: Lab Processing Flow Sheet/Template for Specimen Collection

Appendices: OPTIONAL

Add any desired appendices, remember to update the "OPTIONAL" with the correct description.

To create a new appendix:

- Insert a page break after each new appendix by Clicking Insert, Selecting "Break", Select "Selection break types", Click "Next page", Click "Ok"
- Once the new page is created, insert the new section header by copying and pasting the new section header, on the new page, from the previous section header, e.g., "Appendices: OPTIONAL":
    - Scroll to the "Appendices: OPTIONAL"
    - Click and drag over the section header **Appendices: OPTIONAL**
    - On the tool bar, Click (copy)
    - Then scroll down to the new section (blank page)
    - On the tool bar, Click (paste)
    - Click (save).
- Rename the "OPTIONAL" with the new appendix name:
    - Click and drag over the section header **Appendices: OPTIONAL**
    - Type the new name of the appendix.
    - Click (save).
- To update the Table of Contents (TOC) to include the new appendix(es):
    - Scroll or Page-up to the TOC.
    - Right-click somewhere in the TOC, it will highlight gray.
    - A pop-up menu will appear, Select Update Field.
    - To grab the new appendices, Select Update entire table.
    - Click (save).

For assistance with problems relating to the Table of Contents or any of these instructions, please feel free to contact Heather Bridge at 301-451-2419.